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Feline large granular lymphocyte lymphoma: An Italian Society of Veterinary Oncology (SIONCOV) retrospective study

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Feline large granular lymphocyte (LGL) lymphoma is an uncommon subtype of lymphoma characterized by a grave prognosis and scarce response to chemotherapy. There are limited reports on clinico-pathological and prognostic factors. One-hundred and 9 cats with newly diagnosed LGL lymphoma that underwent initial staging (including hematology, serum biochemistry, thoracic radiographs and abdominal ultrasound), and followed-up were retrospectively evaluated. LGL lymphoma was localized within the gastrointestinal tract with or without extra-intestinal involvement in 91.7% of the cases, and at extra-gastrointestinal sites in 8.3%. Symptoms were frequent. Anemia (31.2%) and neutrophilia (26.6%) were commonly observed, and 14 (12.8%) cats had neoplastic circulating cells. Frequent biochemistry abnormalities included elevated ALT (39.4%) and hypoalbuminemia (28.4%). Twenty (54.1%) of 37 cats had elevated serum LDH. Treatment varied among cats, and included surgery (11%), chemotherapy (23%), corticosteroids (38.5%) and no treatment (27.5%). Median time to progression (MTTP) was 5 days, and median survival time (MST) 21 days. MST was significantly shorter in the case of substage b, circulating neoplastic cells, lack of chemotherapy administration, and lack of treatment response. A small subset of cats (7.3%) survived more than 6 months, suggesting that a more favorable clinical course can be found among LGL lymphoma patients.

KEYWORDS

feline, large granular lymphocyte, LGL, lymphoma, prognosis

1 | INTRODUCTION

Feline large granular lymphocyte (LGL) lymphoma is a relatively rare, morphologically distinct subtype of lymphoma that, among pets, is mainly diagnosed in the feline specie. The origin of LGL lymphoma has been linked to cytotoxic T- or NK lymphocytes, as documented by positive immunoreactivity to T-cell or perforin-like markers.[1]

Systematic data on clinical characteristics, type of treatment, and outcome in large cohorts of cats with LGL lymphoma are rare and all reported series relatively small, with the largest study involving 45 cats.[2] According to the published literature, LGL lymphoma occurs more commonly in the small intestine, with a tendency to involve the regional lymph nodes, other abdominal organs, peripheral blood and/or bone marrow.[2]

There has been no substantial improvement in outcome over the last 2 decades. In fact, all published studies show poor survival times compared to other lymphoma subtypes, typically in the range of few months, with scarce response to cytotoxic chemotherapy.[2–5] Due to the poor outcome and the presence of severe clinical signs, euthanasia is usually carried out soon after diagnosis.[2–5] Nevertheless, treated individual cases are occasionally described as harboring a more favorable prognosis.[2,3,6]

The aim of this retrospective study was to gather broader clinico-pathological information on feline LGL lymphoma, which could

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be used to better define prognosis and improve the treatment decision process for this rare disease entity.

2 | MATERIAL AND METHODS

Members of the Italian Society of Veterinary Oncology (SIONCOV) were asked to retrospectively search their records to identify cats with newly diagnosed LGL lymphoma without any previous antineoplastic treatment history for the disease (excluding steroids), for which medical record information was sufficient to assess the extent of involvement, treatment, treatment response and outcome. To be enrolled, cats had to have at least a complete blood cell count (CBC), serum biochemistry, thoracic radiographs and abdominal ultrasound.

Results of laboratory testing were classified as normal or abnormal by comparing the results with the reference range of that particular laboratory.

For all cases, the cytological diagnosis of LGL lymphoma relied on the presence of lymphoblasts containing the characteristic intracytoplasmic azurophilic granules, as previously described.[7]

Background information sought included: signalment (breed, sex, age, weight), FIV/FeLV status, clinical signs and duration of signs, corticosteroids administered before diagnosis, staging tests performed, involved sites, serum albumin, serum lactate dehydrogenase (LDH), method of diagnosis, type of treatment, clinical response to treatment, time to progression (TTP), survival time (ST), chemotherapy-related toxicity graded according to VCOG criteria,[8] and cause of death.

Since remission status is a time-varying variable, and serial follow-up imaging in the face of a fatal disease such as LGL may be unrealistic, clinical response to treatment was mainly assessed physically. Thus, cats were divided into responders and non-responders based on physical examination and clinical signs; imaging and laboratory findings were integrated if available. Responders were defined as cats experiencing an improvement or resolution of clinical signs after having started treatment coupled with complete remission and partial remission (if imaging was performed), whereas non-responders were defined as cats experiencing no symptom improvement and/or stable disease or progressive disease (if imaging was performed). All responses were required to last for at least 28 days.

3 | STATISTICAL ANALYSIS

TTP was calculated from the date of diagnosis to the date of first-documented loco-regional and/or distant tumor progression. ST was calculated from the date of diagnosis to the date of last visit or death. Cats alive at data analysis closure or dead due to LGL-unrelated causes were censored.

The following factors were investigated for prognostic significance: breed, age, sex, weight, FIV/FeLV status, substage, symptom duration, administration of corticosteroids before diagnosis, hematological alterations (anemia, neutrophilia, thrombocytopenia, hypoalbuminemia, increased LDH), tumor location (involved gastrointestinal tract, extra-gastrointestinal sites, hepatosplenic involvement, thoracic involvement, cavitary effusion, circulating large granular lymphocytes, bone marrow infiltration), type of treatment (enterectomy, chemotherapy, corticosteroids, no treatment) and clinical response to treatment.

The influence of these factors on TTP and ST was investigated with a univariate and multivariate Cox regression analysis. Median TTP and ST were assessed by means of Kaplan-Meier survival plots.

Statistical analysis was performed with SPSS Statistics v.19 (IBM, Somers, New York). Significance was set at $P \leq .05$.

4 | RESULTS

A total of 109 cats with LGL lymphoma were retrospectively included. There were 90 (82.6%) domestic shorthair cats, 7 (6.4%) Chartreux, 3 (2.8%) Persians, 3 (2.8%) Siamese cats, 2 (1.8%) Angora cats, 2 (1.8%) Bengal cats, 1 (0.9%) Ragdoll and 1 (0.9%) Tonkinese. There were 62 (56.9%) males and 47 (43.1%) females, all of which were neutered. Median age was 10 years (range, 1-17 years), and median weight was 3.8 kg (range, 2-8 kg). All cats have been tested for FIV and FeLV: 3 (2.8%) cats were FeLV positive, and 2 (1.8%) were FIV positive.

One-hundred and 7 (98.2%) cats had been experiencing symptoms for a median of 14 days (range, 1-270 days) before diagnosis. Two (1.8%) cats were asymptomatic, whereas the information was not available for 1 (0.9%) cat. Presenting symptoms are listed in Table 1. Decreased appetite and anorexia were the most common complaints, followed by vomiting, weight loss and lethargy/depression. Eighty-nine (83.9%) cats had more than 1 symptom before diagnosis.

Nineteen (17.4%) cats had received corticosteroids before diagnosis.

LGL lymphoma was diagnosed by means of cytology in 91 (83.5%) cats, and by means of cytology and histopathology in 18 (16.5%) cats (Figure 1). A T-cell immunophenotype was established in 19 tumors (in 17 cases by means of immunohistochemistry and in 2 cases by flow cytometric analysis), whereas the information

TABLE 1 Presenting symptoms of 107 symptomatic cats diagnosed with LGL lymphoma. Eighty-nine cats had more than 1 symptom before diagnosis

Symptom	*n* (%)
Decreased appetite/anorexia	70 (66)
Vomiting	55 (51.9)
Weight loss	49 (46.2)
Diarrhea	21 (19.8)
Lethargy/depression	20 (18.9)
Icterus	10 (9.4)
Polyuria/ polydipsia	5 (4.7)
Dyspnea	4 (3.8)
Stypsis	4 (3.8)
Fever	2 (1.9)
Hematemesis	1 (0.9)
Hematochezia	1 (0.9)
Hypothermia	1 (0.9)

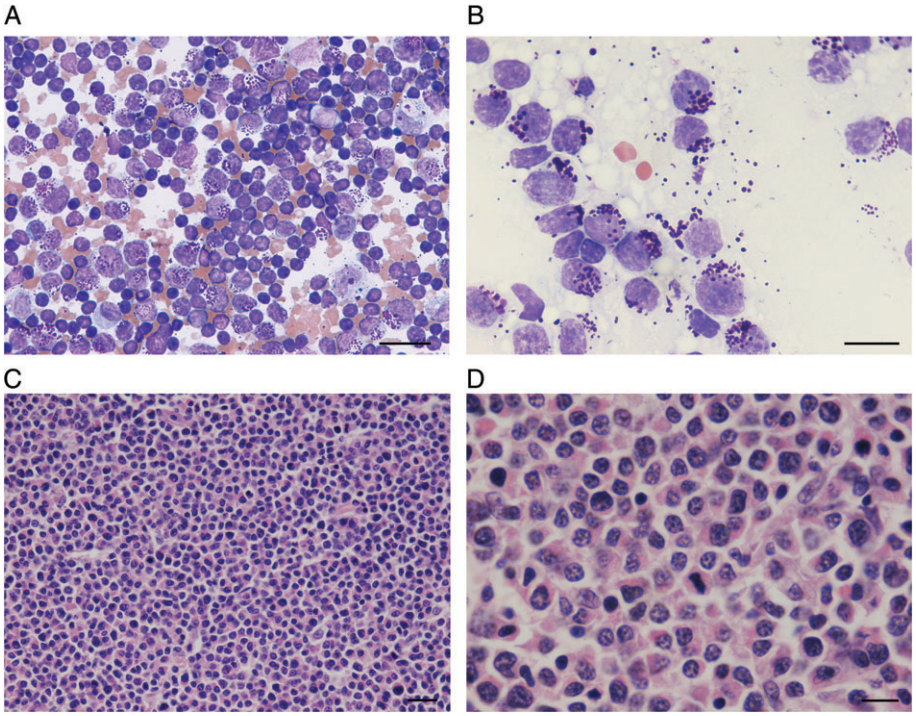

FIGURE 1 Cat, mesenteric lymph node, large granular lymphocyte lymphoma. (A, B) Fine-needle aspirate showing a proliferation of intermediate size lymphocytes, many of which contain coarse purple intracytoplasmic granules at 1 pole of the cell (May Grünwald-Giemsa). (D, E) In the corresponding histological sample, the neoplastic cells show a moderate amount of brightly eosinophilic cytoplasm, but granules are not visible (Hematoxylin and eosin). Bars, 50 μm (A, C) and 25 μm (B, D)

was not available for all other cases. Notably, cytoplasmic granules were not discerned in any case on hematoxylin and eosin-stained tissue sections.

All cats had a minimum database, including CBC, serum biochemistry, thoracic radiographs and abdominal ultrasound.

When considering the CBC, 34 (31.2%) cats were anemic, 29 (26.6%) cats had neutrophilia, 13 (11.9%) had thrombocytopenia, 9 (8.3%) had lymphopenia, 7 (6.4%) had thrombocytosis, 4 (3.7%) had neutropenia, 2 (1.8%) had eosinophilia, 1 (1.8%) had monocytosis and 1 (0.9%) had basophilia. In 14 (12.8%) cats, neoplastic cells were identified in the peripheral blood. In 37 (33.9%) cats, the bone marrow was also examined, and 4 of them had neoplastic involvement. One cat had marrow involvement and no circulating neoplastic cells. Forty-4 (40.4%) cats had no hematological abnormalities.

The most common serum biochemistry abnormalities included elevated alanine aminotransferase activity (n = 43; 39.4%), hypoalbuminemia (n = 31; 28.4%), elevated aspartate aminotransferase activity (n = 30; 27.5%), elevated alkaline phosphatase activity (n = 26; 23.9%), azotaemia characterized by increased blood urea nitrogen or creatinine, or both, (n = 23; 21.1%), hyperbilirubinaemia (n = 20; 18.3%), elevated glutamyltransferase activity (n = 14; 12.8%), and hypocalcemia (n = 13; 11.9%). Twenty (54.1%) of the 37 cats in which serum LDH was checked, had high serum levels. Forty cats (36.7%) had no biochemical abnormalities.

LGL lymphoma was localized within the gastrointestinal tract with or without extra-intestinal involvement in 100 (91.7%) cats, and at extra-gastrointestinal sites in 9 (8.3%) cats.

Within the gastrointestinal tract, LGL lymphoma was localized to the small intestine only (n = 88), large intestine only (n = 1), small and large intestine (n = 8), stomach, small and large intestine (n = 1), stomach and small intestine (n = 1), stomach and large intestine (n = 1). Among the 100 cats with gastrointestinal LGL lymphoma, 85 had also extra-gastrointestinal involvement, including abdominal lymph nodes (n = 73), liver (n = 34), spleen (n = 21), kidneys (n = 8), lung and/or thoracic lymph nodes (n = 11), peripheral lymph nodes (n = 2), skin (n = 1), pericardium (n = 1), and pancreas (n = 1). Ten cats had peritoneal effusion, and 2 cats had pleural effusion.

When considering the 9 cats with extra-gastrointestinal LGL lymphoma, the disease was localized in the liver and spleen in 5 cats, in the liver only in 2 cats, in the kidneys in 1 cat, and in the trachea in 1 cat.

Among the 13 cats with circulating neoplastic cells, 10 had gastrointestinal LGL lymphoma and 3 had extra-gastrointestinal LGL lymphoma.

Twelve (11%) cats underwent enterectomy; 9 of them received CHOP-based dose-intense chemotherapy thereafter, 2 cats received corticosteroids, and 1 cat received no further treatment. Twenty (18.3%) cats received a CHOP-based dose-intense chemotherapeutic protocol and 5 (4.7%) cats were treated with lomustine. Forty-2 (38.5%) cats received corticosteroids as single agent, and 30 (27.5%) cats received no treatment at all.

The overall median TTP was 5 days (95% CI, 2.3-7.6). All cats but 1 was dead at data analysis closure due to their LGL lymphoma with a median ST of 21 days (95% CI, 10.8-31.2). One cat was alive 70 days after diagnosis and was receiving no treatment.

All cats receiving some form of treatment (n = 79) were evaluable for response: 28 (35.4%) cats were considered responders, and the remaining 51 (64.6%) non-responders.

When stratified according to treatment, cats undergoing enterectomy survived for a median of 42 days (95% CI, 4.6-79.3). Cats receiving CHOP-based chemotherapy had a median survival time of 60 days (95% CI, 53.0-67.0), and those receiving lomustine of 90 days (95% CI, 47.0-132.9). Cats treated with corticosteroids had a median survival time of 15 days (95% CI, 9.4-20.6), while those receiving no treatment at all survived for a median of 5 days (95% CI, 0-13.8) (P < .001; Figure 1).

TABLE 2 Univariate Cox regression analysis of variables potentially associated with increased risk of disease progression in 109 cats with LGL lymphoma

Parameter	Median time to progression (days)	HR	95% CI Lower	95% CI Upper	P
Purebred		1.250	0.758	2.063	.382
No	1				
Yes	23				
Sex		1.074	0.731	1.577	.717
Female	1				
Male	7				
Age		1.190	0.811	1.745	.373
>10 years[a]	1				
≤10 years	5				
Weight		1.384	0.934	2.051	.105
≤3.8 kg[a]	1				
>3.8 kg	7				
FIV/FeLV status		1.571	0.633	3.897	.330
Positive	1				
Negative	5				
Symptoms duration		1.092	0.742	1.608	.655
≤14 days[a]	1				
>14 days	7				
Substage		3.091	1.098	8.698	.033*
b	1				
a	70				
Corticosteroids pre-diagnosis		1.416	0.857	2.340	.175
Yes	1				
No	14				
Anemia		1.196	0.791	1.806	.396
Yes	1				
No	10				
Neutrophilia		1.204	0.780	1.860	.401
Yes	1				
No	5				
Thrombocytopenia		1.142	0.637	2.049	.656
Yes	1				
No	7				
Hypoalbuminemia		1.306	0.856	1.992	.216
Yes	1				
No	14				
Increased LDH		2.192	1.065	4.509	.033*
Yes	1				
No	25				
Gastrointestinal tract involvement		1.410	0.707	2.813	.330
No	1				
Yes	5				
Large intestine and/or gastric involvement		1.799	0.977	3.311	.059
Yes	1				
No	10				
Hepatosplenic involvement		1.035	0.706	1.518	.861
Yes	1				
No	10				
Thoracic involvement		1.029	0.550	1.925	.929
Yes	1				
No	7				
Cavitary effusion		1.051	0.573	1.930	.872
Yes	1				
No	7				
Circulating neoplastic cells		1.773	0.993	3.165	.053
Yes	1				
No	10				
Bone marrow infiltration		1.432	0.493	4.161	.509
Yes	15				
No	5				
Enterectomy		1.502	0.818	2.760	.190
No	1				
Yes	34				
Chemotherapy		3.398	2.114	5.461	<0.001*
No	1				
Yes	50				
Response to medical treatment		29.992	9.854	91.284	<0.001*
No	1				
Yes	80				

*Significant *P* value.

[a] Median value.

When considering the 34 cats receiving chemotherapy, treatment-related toxicity was only rarely reported. Altogether, there were 3 episodes of grade 1 and grade 2 gastrointestinal toxicity, respectively; 2 episodes of grade 1 neutropenia, and 4 episodes of grade 2 neutropenia. One cat developed a tumor lysis syndrome after the first vincristine administration, as demonstrated by clinical signs and laboratory results. Twenty-four (70.6%) cats experienced no side effects.

On univariate analysis, factors significantly associated with an increased risk of tumor progression were substage b, increased LDH, lack of chemotherapy administration (either CHOP-based or lomustine) and lack of response to medical treatment (Table 2). On multivariate analysis, only chemotherapy administration was still significant (Table 3).

On univariate analysis, factors significantly associated with an increased risk of tumor-related death were substage b, presence of circulating neoplastic cells, lack of chemotherapy administration, and lack of response to medical treatment (Table 4). On multivariate analysis, both circulating neoplastic cells ($P = .05$) and chemotherapy administration ($P < .001$) retained significance (Table 5).

TABLE 3 Multivariate Cox regression analysis of variables potentially associated with increased risk of disease progression in 109 cats with LGL lymphoma

		95% CI		
	HR	Lower	Upper	*P*
Substage b	3.495	0.452	27.047	.231
Increased LDH	1.393	0.644	3.012	.400
Chemotherapy administration	2.933	1.278	6.729	.011*

*Significant *P* value.

There were 8 (7.3%) cats that survived more than 6 months: all of them had a small intestine LGL with no peripheral blood involvement, and 6 of them (75%) received a CHOP-based protocol. In the population of cats surviving less than 6 months, the concomitant presence of these 3 conditions was only observed in 20 out of 101 cases (19.8%; *P* = .002).

TABLE 4 Univariate Cox regression analysis of variables potentially associated with increased risk of tumor-related death in 109 cats with LGL lymphoma

Parameter	Median survival (days)	HR	95% CI Lower	95% CI Upper	*P*
Purebred		1.280	0.767	2.137	0.344
No	21				
Yes	29				
Sex		1.165	0.788	1.721	0.433
Female	20				
Male	24				
Age		1.160	0.789	1.707	0.450
>10 years[a]	17				
≤10 years	24				
Weight		1.141	1.338	0.908	1.971
≤3.8 kg[a]	20				
>3.8 kg	24				
FIV/FeLV status		1.072	0.435	2.640	0.880
Positive	30				
Negative	21				
Symptoms duration		1.043	0.709	1.534	0.830
≤14 days[a]	21				
>14 days	21				
Substage		3.678	1.151	11.754	0.028*
b	20				
a	210				
Corticosteroids pre-diagnosis		1.507	0.909	2.500	0.112
Yes	15				
No	29				
Anemia		1.377	0.911	2.082	0.130
Yes	21				
No	21				
Neutrophilia		1.245	0.800	1.938	0.332
Yes	21				
No	20				
Thrombocytopenia		1.327	0.739	2.383	0.344
Yes	10				
No	21				
Hypoalbuminemia		1.290	0.846	1.968	0.237
Yes	10				
No	24				
Increased LDH		1.788	0.891	3.588	0.102
Yes	10				
No	37				
Gastrointestinal tract involvement		1.742	0.873	3.475	0.115
No	5				
Yes	21				
Large intestine and/or gastric involvement		1.483	0.795	2.764	0.215
Yes	10				
No	29				
Hepatosplenic involvement		1.106	0.753	1.623	0.608
Yes	20				
No	21				
Thoracic involvement		1.129	0.602	2.115	0.705
Yes	10				
No	24				
Cavitary effusion		1.021	0.533	1.957	0.949
Yes	10				
No	24				
Circulating neoplastic cells		2.136	1.194	3.823	0.011*
Yes	5				
No	24				
Bone marrow infiltration		1.419	0.487	4.131	0.521
Yes	30				
No	30				
Enterectomy		1.375	0.750	2.519	0.303
No	17				
Yes	42				
Chemotherapy		2.671	1.740	4.100	<0.001*
No	14				
Yes	63				
Response to medical treatment		13.899	6.749	28.623	<0.001*
No	15				
Yes	101				

*Significant *P* value.

[a] Median value.

5 | DISCUSSION

This study represents the largest clinical study of feline LGL lymphoma, a rare lymphoproliferative disease characterized by clonal

TABLE 5 Multivariate Cox regression analysis of variables potentially associated with increased risk of tumor-related death in 109 cats with LGL lymphoma

		95% CI		
	HR	Lower	Upper	*P*
Substage b	2.966	0.932	9.439	0.066
Circulating neoplastic cells	1.794	1.000	3.221	0.050*
Chemotherapy administration	2.483	1.613	3.821	<0.001*

*Significant *P* value.

expansion of cytotoxic T- or NK lymphocytes, as described in the WHO histological classification of hematopoietic tumors of domestic animals in 2002.[9] Due to its rarity, LGL lymphoma is the poorest characterized malignancy among lymphoid neoplasms, and the clinical features have been described only in a small subset of studies. In general, feline LGL lymphoma is perceived as a catastrophic disease with an almost uniform mortality, for which no standard treatment is currently available. In 2008, it was documented that cats with LGL lymphoma typically die within 2 months despite treatment with dose-intense chemotherapy.[2] More recently, 9 cats with LGL lymphoma receiving lomustine with or without L-Asparginase had a median ST of 129 days.[10]

In our cohort of 109 cats with LGL lymphoma, the median age of diagnosis was 10 years. Domestic shorthair cats were over-represented, and the overall incidence was similar between males and females.

We confirm that cats with LGL lymphoma suffer from a very poor prognosis with a median TTP of 5 days and a median ST of 21 days. In agreement with previous studies, LGL lymphoma was most commonly located in the small intestine, abdominal lymph nodes and liver.[2,11] While the characteristic granules within lymphocytes were easily recognized by cytological evaluation in all cases, histopathology failed to reveal discernible cytoplasmic granules, thereby highlighting the pivotal role of cytology in diagnosing this rare entity.

In the current series, symptoms and signs typically occurred acutely, and cats experienced rapid disease progression and deteriorating condition. As previously reported[2], non-specific signs such as decreased appetite or anorexia, vomiting, weight loss, diarrhea and lethargy were commonly described. The presence of symptoms (substage b) was significantly associated with shorter TTP and ST; nevertheless, only 2 cats were asymptomatic and this may have biased the results. Substage b has been already reported as a negative prognostic factor,[12–15] as it probably reflects the poor tolerance to dose-intense chemotherapy, leading to sub-optimal dosing and/or a premature treatment interruption, and the unwillingness of the owner to pursue any treatment.

While hematological and biochemical abnormalities were quite common, accounting for >50% of cats, none of them beside increased LDH serum levels and circulating neoplastic cells reached prognostic significance.

LDH is a cytoplasmic enzyme involved in anaerobic glycolysis that reversibly catalyzes the transformation of pyruvate to lactate and protons. The acidity generated by lactate and protons stimulates cancer invasiveness and metastatic dissemination, leading to chemoresistance and poor outcome.[16] High serum LDH predicts short survival in human diffuse large B-cell lymphoma and is 1 of the 5 risk factors included in the International Prognostic Index.[17] Similarly, increased serum LDH levels detected before and after treatment have been shown to correlate with decreased survival in cats and dogs with lymphoma.[18–20] In this series, increased LDH was significantly associated with a higher risk of disease progression, supporting the evaluation of serum LDH level as a prognostic marker for cats with LGL lymphoma.

Circulating neoplastic cells were significantly associated with a shorter ST after univariate and multivariate analysis. Thus, the presence of circulating neoplastic cells was associated with disseminated disease, correlating with significantly worse prognosis.

Nine of the 14 cats with circulating neoplastic cells had also their bone marrow checked, and 4 of them had marrow infiltration. For those cats without microscopic evidence of bone marrow infiltration, the presence of a leukemic phase was likely a consequence of overspill of neoplastic LGL cells from visceral sites. Although lymphoma overspill is an uncommon and poorly investigated phenomenon in veterinary medicine, this is anecdotally reported mainly in patients with gross tumor burden.[21,22]

The remaining 5 cats did not receive a bone marrow aspirate; therefore, further comments would be speculative. One cat without circulating neoplastic cells had bone marrow infiltration.

No standardized treatments are currently available to treat cats with LGL lymphoma, and the optimal therapy remains unclear. In general, treatment strategies consist of palliative medical treatment, surgery, chemotherapy, or a combination of these, each applied depending on the eligibility of the cat.

The greatest majority of the cats described here received either corticosteroids as single agent or no treatment at all. Unlike dogs, prior treatment with steroids did not impact prognosis in this series of cats, and this is in agreement with a previous study.[23] In our opinion, this conservative approach may have been the result of clinicians' skepticism and owner demotivation. In fact, the reported grave prognosis together with the high incidence of gastrointestinal signs at presentation (weight loss and anorexia) has likely discouraged owners and clinicians form pursuing a more aggressive treatment approach.

Nevertheless, beside palliative treatment with steroids, a range of therapeutic strategies has been used in the current series.

It has been described that individual cats can benefit from surgery;[24,25] however, this was not confirmed in the present cases. Indeed, 12 cats underwent surgical debulking, followed by subsequent chemotherapy in 9 of them, with no significant improvement of outcome. It may be possible that tumor resection does not benefit cats with LGL lymphoma due to its peculiar biology, as previously described,[6,26–29] or the small number of cats may have rendered the results statistically not significant.

In a previous study, LGL lymphoma has shown poor response to standard chemotherapy regimens consisting of CHOP,[2] while the outcome was slightly better if lomustine with or without L-asparaginase was administered.[10] In the current series, lack of chemotherapy administration (either CHOP-based or lomustine) was significantly associated with tumor progression and tumor-related death on uni- and multivariate analysis. Additionally, lack of response to

medical treatment was significantly associated with tumor progression and tumor-related death, as already reported.[23,26,29–31] It must be stressed that despite the improvement in survival duration, responses did not last, with a median survival time in cats receiving chemotherapy of only 63 days, thereby revealing a very limited success of medical treatment. Cats receiving lomustine as single agent had a median ST of 90 days. Although this represents a minimal improvement in survival duration, the efficacy of lomustine should be evaluated in future prospective trials.

Notably, there were 8 cats surviving more than 6 months, suggesting that the clinical behavior of these LGL lymphomas differs from the typical clinical course. It was not possible to identify characteristics unique to this sub-population; however, all the 8 cats had a small intestine LGL with no peripheral blood involvement and 6 of them had been treated with a CHOP-based protocol. Therefore, cats with a more favorable clinical course can be found among LGL lymphoma patients. Additional studies should be performed to compare the histological and molecular features of these tumors with those of the more aggressive cases.

Also, no definitive distinction exists between LGL leukemia or lymphoma in cats, where the 2 diseases often overlap, presenting a similar aggressive behavior, regardless if originating from T cytotoxic (CD3+/CD8+) or NK lymphocytes. The clinical presentation and the poor prognosis reported by previous studies and in our population recall that of human patients with LGL lymphoproliferative disorders of NK rather than CD3+/CD8+ phenotype; in the latter, in fact, an indolent behavior and a favorable outcome can be expected. Conversely, in dogs, the prognostic role of phenotype remains unclear in LGL leukemias and lymphoma, as these tend to have an indolent course with lymphocytosis lasting months to years. However, some dogs with LGL lymphomas may undergo a more rapid progression leading to a grave outcome.[32]

This study has some limitations, including its retrospective nature impeding the ability to access individual data and preventing treatment standardization, and the subjective response assessment that may have biased the classification of responders and non-responders. Nevertheless, all cats had internal disease and serial imaging studies were deemed impractical and expensive, more over in the face of a rapidly fatal disease. Strength of the present study was that all cats underwent initial staging, including thoracic radiographs and abdominal ultrasound, and none was lost to follow-up.

In conclusion, this study has identified the largest group of feline LGL lymphoma published so far. The high mortality of LGL lymphoma was associated not only with the very aggressive and often chemotherapy-refractory nature of the disease, but also to the poor condition of cats due to prolonged presence of severe symptoms, possibly compromising the ability to deliver dose-intense chemotherapy and/or to pursue aggressive surgery. Further negative prognostic factors included circulating neoplastic cells, high LDH levels, lack of chemotherapy administration, and lack of response to medical treatment. A small subset of cats had a more indolent disease course with survival times exceeding 6 months. Based on the above, we hypothesize that chemotherapy in the form of CHOP-based protocols or CCNU as single agent may improve disease control and survival. Future prospective studies are warranted to uniform therapy recommendations.

REFERENCES

1. Kariya K, Konno A, Ishida T. Perforin-like immunoreactivity in four cases of lymphoma of large granular lymphocytes in the cat. *Vet Pathol*. 1997;34:156-159.
2. Krick EL, Little L, Patel R, et al. Description of clinical and pathological findings, treatment and outcome of feline large granular lymphocyte lymphoma (1996–2004). *Vet Comp Oncol*. 2008;6:102-110.
3. Sapierzyński R, Jankowska U, Jagielski D, Kliczkowska-Klarowicz K. Large granular lymphoma in six cats. *Pol J Vet Sci*. 2015;18:163-169.
4. Darbès J, Majzoub M, Breuer W, Hermanns W. Large granular lymphocyte leukemia/lymphoma in six cats. *Vet Pathol*. 1998;35:370-379.
5. Wellman ML, Hammer AS, DiBartola SP, Carothers MA, Kociba GJ, Rojko JL. Lymphoma involving large granular lymphocytes in cats: 11 cases (1982–1991). *J Am Vet Med Assoc*. 1992;201:1265-1269.
6. Wolfesberger B, Skor O, Hammer SE, et al. Does categorisation of lymphoma subtypes according to the World Health Organization classification predict clinical outcome in cats? *J Feline Med Surg*. 2016; pii:1098612X16666119.
7. Roccabianca P, Vernau W, Caniatti M, Moore PF. Feline large granular lymphocyte (LGL) lymphoma with secondary leukemia: primary intestinal origin with predominance of a CD3/CD8 (alpha)(alpha) phenotype. *Vet Pathol*. 2006;43:15-28.
8. Veterinary Co-operative Oncology Group. Veterinary Co-operative oncology group- common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol*. 2004;2:194-213.
9. Valli VE, Jacobs RM, Parodi AL, Verneau W. *Histological Classification of Hematopoietic Tumors of Domestic Animals*. Vol VIII. Washington, DC: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center; 2002.
10. Rau SE, Burgess KE. A retrospective evaluation of lomustine (CeeNU) in 32 treatment naïve cats with intermediate to large cell gastrointestinal lymphoma (2006–2013). *Vet Comp Oncol*. 2016;9. https://doi.org/10.1111/vco.12243.
11. Cesari A, Bettini G, Vezzali E. Feline intestinal T-cell lymphoma: assessment of morphologic and kinetic features in 30 cases. *J Vet Diagn Invest*. 2009;21:277-279.
12. Waite AH, Jackson K, Gregor TP, Krick EL. Lymphoma in cats treated with a weekly cyclophosphamide-, vincristine-, and prednisone-based protocol: 114 cases (1998–2008). *J Am Vet Med Assoc*. 2013;242:1104-1109.
13. Mahony OM, Moore AS, Cotter SM, Engler SJ, Brown D, Penninck DG. Alimentary lymphoma in cats: 28 cases (1988–1993). *J Am Vet Med Assoc*. 1995;207:1593-1598.
14. Vail DM, Moore AS, Ogilvie GK, Volk LM. Feline lymphoma (145 cases): proliferation indices, cluster of differentiation immunoreactivity, and their association with prognosis in 90 cats. *J Vet Intern Med*. 1998;12:349-354.
15. Mooney SC, Hayes AA, MacEwen EG, Matus RE, Geary A, Shurgoy BA. Treatment and prognostic factors in lymphoma in cats: 103 cases (1977–1981). *J Am Vet Med Assoc*. 1989;194:696-699.
16. Peppicelli S, Bianchini F, Calorini L. Extracellular acidity, a "reappreciated" trait of tumor environment driving malignancy: perspectives in diagnosis and therapy. *Cancer Metastasis Rev*. 2014;33:823-832.
17. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2014;123:837-842.
18. Hadden AG, Cotter SM, Rand W, Moore AS, Davis RM, Morrissey P. Efficacy and toxicosis of VELCAP-C treatment of lymphoma in cats. *J Vet Intern Med*. 2008;22:153-157.
19. Marconato L, Crispino G, Finotello R, Mazzotti S, Zini E. Clinical relevance of serial determinations of lactate dehydrogenase activity used to predict recurrence in dogs with lymphoma. *J Am Vet Med Assoc*. 2010;236:969-974.
20. Zanatta R, Abate O, D'Angelo A, Miniscalco B, Mannelli A. Diagnostic and prognostic value of serum lactate dehydrogenase (LDH) and LDH isoenzymes in canine lymphoma. *Vet Res Commun*. 2003;27(Suppl 1):449-452.

21. Martini V, Marconato L, Poggi A, et al. Canine small clear cell/T-zone lymphoma: clinical presentation and outcome in a retrospective case series. *Vet Comp Oncol*. 2016;14(Suppl 1):117-126. https://doi.org/10.1111/vco.12155.
22. Marconato L, Gelain ME, Comazzi S. The dog as a possible animal model for human non-Hodgkin lymphoma: a review. *Hematol Oncol*. 2013;31:1-9. https://doi.org/10.1002/hon.2017.
23. Gustafson TL, Villamil A, Taylor BE, Flory A. A retrospective study of feline gastric lymphoma in 16 chemotherapy-treated cats. *J Am Anim Hosp Assoc*. 2014;50:46-52.
24. Gouldin ED, Mullin C, Morges M, et al. Feline discrete high-grade gastrointestinal lymphoma treated with surgical resection and adjuvant CHOP-based chemotherapy: retrospective study of 20 cases. *Vet Comp Oncol*. 2017;15:328-335.
25. Malik R, Gabor LJ, Foster SF, McCorkell BE, Canfield PJ. Therapy for Australian cats with lymphosarcoma. *Aust Vet J*. 2001;79:808-817.
26. Zwahlen CH, Lucroy MD, Kraegel SA, Madewell BR. Results of chemotherapy for cats with alimentary malignant lymphoma: 21 cases (1993–1997). *J Am Vet Med Assoc*. 1998;213:1144-1149.
27. Collette SA, Allstadt SD, Chon EM, Vernau W, Smith AN, Garrett LD. Treatment of feline intermediate- to high-grade lymphoma with a modified university of Wisconsin-Madison protocol: 119 cases (2004–2012). *Vet Comp Oncol*. 2016;14(Suppl 1):136-146.
28. Slawienski MJ, Mauldin GE, Mauldin GN, Patnaik AK. Malignant colonic neoplasia in cats: 46 cases (1990–1996). *J Am Vet Med Assoc*. 1997;211:878-881.
29. Fondacaro JV, Richter KP, Carpenter JL, Hart JR, Hill SL, Fettman MJ. Feline gastrointestinal lymphoma: 67 cases (1988–1996). *Eur J Comp Gastroenterol*. 1999;4:5-11.
30. Milner RJ, Peyton J, Cooke K, et al. Response rates and survival times for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol: 38 cases (1996–2003). *J Am Vet Med Assoc*. 2005;227:1118-1122.
31. Teske E, van Straten G, van Noort R, Rutteman GR. Chemotherapy with cyclophosphamide, vincristine, and prednisolone (COP) in cats with malignant lymphoma: new results with an old protocol. *J Vet Intern Med*. 2002;16:179-186.
32. Valli VE, Bienzle D, Meuten DJ. Tumors of the hemolymphatic system. In: Meuten DJ, ed. *Tumors in Domestic Animals*. 5 ed. Ames: John Wiley & Sons; 2016:203-321.

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