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Original research

Feline lymphoma: a pilot study of prevalence and course features

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Abstract. The results of the analysis of the medical histories of 36 cats with lymphoma, a malignant tumor disease of the lymphatic system, are presented. The relevance of the problem is due to the high level of morbidity and mortality, as well as the complexity of lymphoma verification. The multi-vector nature of damage to body systems and tissues due to lymphomas required the use of a wide range of diagnostic measures. The distribution of lymphoma in cats in the conditions of veterinary medicine hospitals of the cities of Dnipro and Zaporizhzhia was studied taking into the account age and breed susceptibility. The structure of feline lymphoma diseases based on its anatomical forms has been established. Changes in general clinical and biochemical blood markers in cats with lymphoma were determined. It was established that in the structure of the incidence of lymphoma in cats, a significant share is occupied by half-breeds (36.1 %) and representatives of Scottish (22.2 %) and British (19.4 %) breeds, aged 8–10 years (36.1 %) and older (33.3 %). It has been shown that the probability of lymphoma in cats increases progressively with age. In the vast majority of cases, alimentary (41.6%) and multicentric (30.6%) forms of lymphoma were verified against the background of a high risk of damage to any tissue or organ. Clinical signs are correlated with anatomical forms of lymphoma, but in the presence of individual features of the disease progression. Lymphoma progress is asymptomatic during the first stage. The analysis of hematological and biochemical markers of the blood of cats with lymphoma confirmed the inhibition of hematopoietic mechanisms and immune protection against the background of signs of intoxication of the body. The degree of violation of biological mechanisms depends on the affected tissues / body systems and accompanying diseases of viral (leukemia, immunodeficiency of cats) and non-infectious (chronic renal failure, enteropathy) etiology. The obtained results confirmed that further research is required to clarify the role of etiological factors (primarily, the external environment), a better understanding the biological mechanisms of initiation and progression of the disease as well as promising therapeutic targets for the treatment of lymphoma in cats.

Keywords: cats; tumor; lymphoma; distribution monitoring; breed and age susceptibility; hematological disorders; biochemical blood changes

Лімфома котів: пілотне дослідження поширення та особливостей перебігу

Анотація. Представлено результати аналізу історій хвороби 36 котів, хворих на лімфому – злоякісне пухлинне захворювання лімфатичної системи. Актуальність проблеми обумовлена високим рівнем захворюваності та летальності, а також складністю верифікації лімфоми. Багатовекторність ураження систем і тканин організму за лімфоми вимагав використання широкого спектру діагностичних заходів. Вивчено поширення лімфоми у котів в умовах лікарень ветеринарної медицини міста Дніпро та Запоріжжя із урахуванням вікової і породної сприйнятливості. Встановлено структуру захворювань котів на лімфому за її анатомічними формами. Визначено зміни загальноклінічних і біохімічних маркерів крові у котів із лімфомою. Встановлено, що в структурі захворюваності котів на лімфому значну частку займають метиси (36.1 %) та представники шотландської (22.2 %) і британської (19.4 %) порід, віком 8–10 років (36.1 %) та старших (33.3 %). Показано, що ймовірність захворювання котів на лімфому прогресивно збільшується із віком. У переважній більшості випадків верифіковано аліментарну (41.6 %) та мультицентричну (30.6 %) форму лімфоми на фоні високого ризику ураження будь-якої тканини або органу. Із анатомічними формами лімфоми корелюють клінічні ознаки, але за наявності індивідуальних особливостей перебігу захворювання. На перших стадіях лімфома перебігає безсимптомно. Аналіз гематологічних та біохімічних показників крові котів із лімфомою засвідчив пригнічення механізмів кровотворення та імунного захисту на фоні ознак інтоксикації організму. Ступінь порушення біологічних механізмів залежить від уражених тканин / систем організму та супутніх захворювань вірусної (лейкемія, імунодефіцит котів) та незаразної (хронічна ниркова недостатність, ентеропатія) етіології. Отримані результати засвідчили необхідність подальших досліджень етіологічних чинників (насамперед, зовнішнього середовища), більш детального вивчення біологічних механізмів ініціації і прогресування захворювання, а також перспективних терапевтичних мішеней для лікування лімфоми у котів.

Ключові слова: коти; пухлини; лімфома; моніторинг поширення; породна і вікова сприйнятливість; гематологічні порушення; біохімічні зміни крові.

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Introduction

Cancer – one of the leading causes of mortality among companion animals. Epidemiological information on cancer is crucial for practicing veterinarians in treating patients. However, spontaneous tumors in companion animals resemble human neoplasms and can provide valuable data for combating malignancies. Veterinary cancer registries for cats are scarce and typically cover only a short timeframe.

Lymphoma, a neoplasm of lymphoid tissue, can manifest with localized or systemic clinical signs. Unlike in dogs, where multicentric disease primarily affects lymphoid organs (lymph nodes), feline lymphoma can present as visceral (spleen/liver/intestine), extranodal (central nervous system/skin), or nodal forms. Clinical signs depend on the affected organ, with intrathoracic, intra-abdominal, subcutaneous, and multicentric forms registering asymptomatic progression during the chronic course (Mason & Pittaway, 2022).

Spontaneous neoplasms in domestic cats are more commonly reported than in dogs and are a major cause of mortality in older animals. Alongside squamous cell carcinoma, sarcoma, and basal cell neoplasms, lymphoma remains prevalent. Overall, the tumor structure in cats includes neoplasms of the skin and soft tissues (55.9% of all tumor types), mammary glands (11%), digestive tract (7.9%), oral cavity and tongue (7.3%), nasal cavity and middle ear (6%), lymph nodes (3.1%), bones (1.8%), and liver/intrahepatic bile ducts (1.3%) (Manuali et al., 2020).

According to Graf et al. (2015), malignant neoplasms in cats account for 80.3%, with an increased likelihood of development with age and a higher risk in females. Malignant tumors of the lymphatic system comprise 21.28% of the total number of neoplasms and, along with epithelial (43.06%) and mesenchymal tumors (27.98%), constitute the top three most common tumors.

Epidemiological data provided by Schmidt et al. (2010) indicate a 70% risk of malignant tumor detection in cats, with lymphoma (22%), soft tissue sarcoma (15%), mast cell tumor (9%), and squamous cell carcinoma (7%) being prevalent. Tumors were classified as hematopoietic (31%); malignant: epithelial (19%), mesenchymal (16%); benign: epithelial (16%), mesenchymal (13%), and others (n=11; 5%), predominantly localized in the skin and soft tissues (41%). There was observed lymphoma prevalence of 48/100000 (95% CI: 44–56/100000) and an incidence of 32/100000 (95% CI: 26–35/100000) (Economu et al. 2021). Male cats exhibited a higher lymphoma risk (OR: 1.7, 95% CI: 1.2–2.4), particularly between the ages of 2 and 5 years (OR: 5.0, 95% CI: 2.8–8.8).

In most cats with lymphoma, changes in morphological and biochemical blood parameters are observed, which correlate with clinical signs and ultrasound findings. Animals exhibit lethargy, loss of appetite, and weight loss alongside non-regenerative anemia and leukocytosis, with changes in the echotexture of lymph nodes and spleen enlargement (Kempen, 2022).

Despite accumulating a certain volume of information regarding lymphoma, questions concerning its etiology, pathogenesis, progression, and prognosis remain insufficiently studied (Marsilio, 2021). The accumulation of clinical, morphological, and histopathological signs of lymphoma significantly complicates disease diagnosis. Furthermore, diseases of the peritoneum, mesentery, and omentum are important causes of morbidity and mortality in both humans and animals, although veterinary literature on the topic is limited.

Although primary neoplasms arising from mesenchymal tissues of the omentum are rare, the omentum of the small intestine is a major route for tumor spread within the peritoneal cavity. Tumors spread to the omentum via four main pathways: direct extension, typically seen with carcinoid tumors of the small intestine, intra-abdominal malignant neoplasms (pancreatic and colorectal cancer); lymphatic dissemination of lymphoma and certain epithelial malignancies; hematogenous dissemination leading to embolic metastases into the wall of the small intestine (melanoma and mammary gland carcinoma); migration across the peritoneum of ovarian and gastrointestinal tract malignancies, as well as certain lymphomas (Sheth et al., 2003).

The most common intestinal neoplasm in cats is low-grade T-cell enteric lymphoma (LGITL), which shares similarities with lymphoplasmacytic enteritis (LPE) in terms of clinical manifestations, laboratory findings (blood, histological, immunohistochemical), and ultrasound studies, as well as signs of clonality. The main differences of lymphoma include the presence of ultrasonographically identified rounded intestinal lymph nodes and abdominal effusion in the context of positive results of their comprehensive histopathological and phenotypic assessment. Additional features of the alimentary form of lymphoma include a higher frequency in males, longer duration of clinical signs, and polyphagia (Freiche et al., 2021).

The incidence rate of low-grade alimentary lymphoma (LGAL) in cats has significantly increased over the past decade, accounting for 60–75% of cases of gastrointestinal lymphoma. Importantly, feline LGAL can be considered a potential animal model for chronic enteropathic T-cell lymphoproliferative disorders, a rare human disease (Paulin et al., 2018).

The alimentary form of lymphoma (AL) requires to be differentiated from food-responsive enteropathy (FRE) and idiopathic inflammatory bowel disease (IBD), which present with chronic gastrointestinal tract (GIT) signs. A definitive diagnosis should be based on invasive diagnostic investigations (Gianella et al., 2017). Lymphoma of the large intestine with involvement of the omentum may present similarly to lymphomatosis, clinically characterized by anorexia, weight loss, and hematochezia; ultrasonographically, it may exhibit heterogeneous hypoechoic transmural thickening of the colon extending beyond the serosal layer into the adjacent omentum; histopathologically, it may be of the B-cell type (Oetelaar et al., 2020).

Lymphomatosis manifests as small hypoechoic nodular lesions on the parietal and/or visceral surfaces of the peritoneum, often accompanied by bilateral renomegaly and secondary local lymphadenopathy (Morgan et al., 2018).

Gastrointestinal and multicentric lymphoma which are diagnosed in cats about of 44.3% cases was assessed as high correlated ($p < 0.001$) with the risk of thrombocytosis (Howard et al., 2023). Thus, there is no single diagnostic criterion or biomarker that allows for the reliable differentiation of inflammatory lesions from neoplastic lymphoproliferations in the gastrointestinal tract of cats. Therefore, the diagnosis is currently established by combining all available clinical and diagnostic data including histopathological results (Marsilio et al., 2023).

The aim of the study was to analyse the prevalence and characteristics of clinical, hematological/biochemical, and pathomorphological changes in cats with lymphoma.

Materials and methods

The study was conducted at the "Best" private veterinary hospital in Zaporizhzhia and the state veterinary hospital of Shevchenkivskyi and Sobornyi districts in Dnipro city, as well as the Department of Veterinary Surgery and Reproductology at Dnipro State Agrarian and Economic University.

The disease histories of 36 cats diagnosed with lymphoma during 2023 were study. The age of the animals was diverse from six months to fifteen years. The cats included mixed-breed, Scottish, British, Bengal, Devon Rex, and Maine Coon breeds. During the first stage, anamnestic data were collected, including the duration

of the illness, clinical signs and their dynamics, feeding and housing regimen, vaccination history, previous diseases, and the effectiveness of previous treatment.

Clinical assessment included the determination of basic parameters (temperature, pulse, respiration), overall condition of the animal, and visual assessment of tissue lesions. Additional study included ultrasound scanning and/or radiography of the thoracic and abdominal cavities, analysis of clinical and biochemical blood parameters, as well as histopathological and immunohistochemical evaluation of functional tissue changes.

Ultrasound analysis and radiography were used to verify the presence of lesions (primary and metastatic) in the thoracic, abdominal, and pelvic cavities. In some cases, ultrasound scanning was used to guide the collection of pathological material through fine-needle biopsy. Contrast agents were used to enhance radiographic images.

Hematological and biochemical blood tests aimed to identify functional and structural abnormalities in systems and organs. Depending on the features of the course of lymphoma, the diagnostic tests of the study were chosen individually.

The samples were separated depending on the nature of the lesion, through laparotomy, excision of pathological foci, puncture biopsy and/or autopsy. Lymphoma tissue samples were isolated to carry out histopathological and immunohistochemical analysis. Histopathological and immunological studies of pathological material were carried out with the aim of verifying the tumor and its differential diagnosis from non-neoplastic lesions. All cases were classified according to WHO criteria (Vezzali et al., 2010; Wolfesberger et al., 2017, 2018).

Statistical analysis and graphical processing of the results carried out with using Statistica 10 software (StatSoft inc., USA, 2011). Obtained data analysed with using the Tukey test, taking into the account the Bonferroni error for multiple comparisons. The significance of differences was considered at $p>0.05$.

Results

The clinical signs of lymphoma in cats exhibited considerable variability, reflecting the involvement of individual systems or organs, or combinations thereof. The pilot study involved study the medical described reports of 36 cats with confirmed diagnosis of "lymphoma."

Among the cats with lymphoma, the absolute majority were mixed-breed, accounting for 36.1% of the disease prevalence (Table 1). Cats of breeds such as Scottish (22.2%), British (19.4%), and Devon Rex (11.1%) were also susceptible to lymphoma. Representatives of Maine Coon and Bengal breeds had a disease prevalence of 6% (5.6%). It is likely that other breeds are also susceptible to lymphoma, considering that the frequency of registration is influenced by their prevalence in specific territories.

Table 1 – Breed susceptibility of cats to lymphomas

Breed belonging	Number of animals	
	n	%
Scottish	8	22.2
British	7	19.4
Devon rex	4	11.1
Maine Coon	2	5.6
Bengali	2	5.6
Metis	13	36.1
Total	36	100

According to the monitoring of lymphoma prevalence, the highest level of incidence is characteristic among cats aged over eight years (Table 2). Among animals aged eight to ten years, the registration frequency of lymphoma is 36.1%, while for those older than ten years, it is 33.3%. Lymphoma diagnosis occurs in 13.9% of cases among cats in the middle age group. In young animals aged up to two years, the proportion of affected animals does not exceed 3%.

Table 2 – Lymphoma frequency occurrence in different age groups of cats

Age groups of cats (years)	Number of animals	
	n	%
< 2	1	2.8
2-5	5	13.9
5-8	5	13.9
8-10	13	36.1
>10	12	33.3
Total	36	100

The analysis of lymphoma incidence in cats, depending on its anatomical classification, revealed the following patterns (Table 3).

The most common form of lymphoma was the alimentary form (characterized by involvement of the gastrointestinal tract), diagnosed in 41.6% of animals. Approximately one-third of lymphoma cases (30.6%) involved multiple organs/tissues (multicentric form). Mediastinal lymphoma in cats which involved tumor foci in the mediastinum was more commonly in the thoracic cavity and was detected in 16.7% of animals. The extranodal form of lymphoma involving the kidneys, skin, and ocular globes was diagnosed in 11.1% of cats.

The blood samples of cats with lymphoma exhibited changes in hematological parameters (Table 4), including a decrease ($p < 0.001$) in hemoglobin, leukocytes, and platelets content by 1.4, 1.7, and 1.3 times, respectively. Moreover, the erythrocyte sedimentation rate was accelerated by 3.3 times ($p < 0.001$).

Analysis of the biochemical profile in cats with lymphoma revealed the following patterns (Table 5). Affected animals showed a significant increase in the content of next mentioned parameters: glucose by 1.4 times ($p < 0.001$), aspartate aminotransferase by 1.6 times ($p < 0.001$), lactate dehydrogenase by 2.1 times ($p < 0.001$), urea by 1.5 times ($p < 0.001$), creatinine by 1.6 times ($p < 0.001$), triglycerides by 1.8 times ($p < 0.001$), and inorganic phosphorus by 2 times ($p < 0.001$). Besides, the decrease in alkaline phosphatase activity by 1.4 times ($p < 0.01$) and gamma-glutamyltransferase by 1.7 times ($p < 0.001$) detected in blood samples.

Table 3 – Anatomical forms of feline lymphoma

Lymphoma types	Number of animals	
	n	%
Alimentary	15	41.6
Multicentric	11	30.6
Mediastinal	6	16.7
Extranodal	4	11.1
Total	36	100

Table 4 – Hematological indicators of blood in cats with lymphoma

Marker	Value		95% CI
	reference	L	
Hemoglobin, g/L	110–180	80.2 ± 8.3***	51–108
Erythrocyte sedimentation rate, mm/h	1–13	42.9 ± 7.6***	15–74
Leukocytes, g/L	6–13	3.5 ± 0.7***	2.9–4.2
Platelets, g/L	190–630	141.2 ± 16.0***	161–177
Erythrocytes, T/l	7.7–12.8	9.3 ± 2.4	6.3–11.6

Note: L – group of animals with lymphoma; *** – $p < 0.001$, compared to reference values

Discussion

The results of lymphoma prevalence monitoring in cats are consistent with corresponding disease incidence rates in other regions. Specifically, according to Geine-Romanova et al. (2023), lymphoma is more frequently registered in mixed-breed cats (67%), of middle age (average age 8 years), with a slight male predominance (56%). Among its anatomical forms, alimentary (53%) and extranodal (38%) lymphomas predominate. In the absolute majority of cases of alimentary lymphoma, transmural foci in the small intestine were verified (88%, 73%). Rogato et al. (2023) identify among the most common forms of lymphoma in cats up to 18 months of age, medium and large cell lymphomas: mediastinal (42%), disseminated (30%), and renal (15%), against the backdrop of a negative test for FIV.

Among lymphomas in cats the most recognized problem is alimentary lymphoma, the differential diagnosis of which, particularly from inflammatory bowel disease is complicated and requires additional investigations: biopsies with immunophenotyping and clonality analysis (Barrs & Beatty, 2012). The lack of tissue specificity against the background of a high frequency of combined lesions of several systems or organs significantly complicates the diagnosis of the disease. Publications dedicated to lymphoma in cats, in most cases, have a descriptive nature without an analytical component. Possible causes discussed include genetic factors, retroviral infections, chronic inflammation, immunosuppression, and passive smoking.

The obtained results confirm the significant prevalence of inflammatory bowel disease (IBD) and alimentary lymphoma (ALA) in cats as well as the complexity of their differential diagnosis, due to the similarity of clinical signs and histopathological characteristics. A promising direction for diagnostic evaluation of IBD and ALA using complete blood count (CBC) and serum chemistry (SC) results is the use of Bayesian classifiers and artificial neural networks (Awaysheh et al., 2016).

Clinical signs depend on the anatomical localization of lymphoma Thus, the preliminary diagnosis can be confirmed by cytological examination results, and the final diagnosis - histopathologically. Currently, there is a correction of the system of pathological classification: replacing the older WF with the

Table 5 – Biochemical profile of cats with lymphoma

Parameter	Value		95% CI
	reference	L	
Glucose, mmol/l	3.2–6.7	9.6 ± 1.5***	7.6–11.2
Total protein, mmol/l	57–79	68.6 ± 6.8	50–86
Albumins, g/L	23–34	26.8 ± 3.9	18–34
Alanine aminotransferase units/l	30–100	56.8 ± 8.4	17–147
Aspartate aminotransferase, units/l	12–56	89.7 ± 4.9***	61.7–122.0
Gamma-glutamyltransferase, units/l	1–9	0.6 ± 0.1***	0.2–0.8
Alkaline phosphatase, units/l	15–92	10.4 ± 1.6**	9.7–13.7
Lactate dehydrogenase, units/l	55–340	723.3 ± 11.5***	649.9–807.9
Urea, mmol/l	6.4–11.8	17.4 ± 2.1***	5.8–21.5
Creatinine, mmol/l	62–159	249.8 ± 20.7***	163–322
Triglycerides, mmol/l	0.1–1.3	2.3 ± 0.2***	1.7–3.3
Total calcium, mmol/l	1.85–2.6	1.9 ± 0.5	1.5–2.9
Inorganic phosphorus, mmol/l	0.8–2.6	5.1 ± 0.6***	4.8–5.9
Chlorides, mmol/l	116–125	116.1 ± 8.7	111.7–129.6
Potassium, mmol/l	4.0–5.3	5.6 ± 1.3	5.3–5.8
Sodium, mmol/l	151–158	163.6 ± 6.5	159.6–167.5

Note: L – group of animals with lymphoma; CI = confidence interval; ** – $p < 0.01$, *** – $p < 0.001$, compared to reference values

new REAL/WHO classification (revised European-American classification of lymphoid neoplasms/World Health Organization). The latter evaluates not only morphology but also immunophenotype of neoplastic cells (Wolfesberger, 2010).

Objectively applied ultrasound criteria are statistically useful for differentiating cytologically determined normal, inflammatory, and neoplastic conditions of the abdomen in dogs and cats. A statistical model based on ultrasound criteria has been proposed, the effectiveness of which ranged from 63.2% to 69.9%. Its combined application with fine-needle biopsy and cytological examinations increased these indicators to 72.3%. Clinical application of ultrasound analysis and cytological methods allowed establishing that regional formations associated with organs, as well as aggregated thickening of the intestines and peritoneum, were more closely associated with peritoneal neoplasia, while localized, highly complex fluid accumulations - with inflammatory peritoneal disease (Feeney et al., 2013).

The absolute majority of oncological diseases are usually accompanied by hematological disorders, including anemia (up to 70% of cases), hypercoagulability, thrombocytopenia, and hyperglobulinemia, while specific tumors are associated with rare anomalies, such as monoclonal gammopathy. Therefore, their detection justifies the search for "hidden" cancer (Childress, 2012).

Finotello et al. (2018) reported anemia (31.2%), neutrophilia (26.6%), hypoalbuminemia (28.4%), as well as elevated alanine aminotransferase (39.4%) and lactate dehydrogenase (54.1%) levels in cats with lymphoma. Despite the presence of certain hematological and biochemical changes in cats with lymphoma (non-regenerative anemia, neutrophilia, lymphocytopenia, eosinopenia, and monocytosis, hypoglycemia, hypoalbuminemia), it has been shown that they have limited diagnostic value. Moreover, breed and gender of the animal, as well as histological and immunophenotypic variations, have a limited impact on laboratory test results (Gabor et al., 2000).

Alimentary lymphoma should be suspected in animals with acute or chronic signs of gastrointestinal disease in the history. For the detection of concomitant diseases, systemic tests such as complete blood count, biochemical analysis of blood, urine analysis, thyroxine level, and chest X-ray are used (Gieger, 2011).

One of the paraneoplastic syndromes associated with non-invasive tumor effects in cats with lymphoma is hypercalcemia, diagnosed in approximately one-third of animals, most commonly with localization in the cranial mediastinum. Serum calcium level is recommended for monitoring the effectiveness of therapeutic measures. Considering the significant biological variability, further research into the stage, anatomical localization, histological grade, and immunophenotype of lymphoma is necessary, as well as a deep analytical assessment of the diagnostic significance of such information (Moore, 2013).

In the near future, genetic studies will become particularly relevant, providing information for a better understanding of the oncogenic mechanisms for different cancer types, including lymphoma (Ludwig et al., 2022). Thus, lymphoma in cats is one of the common neoplasm in the hematopoietic system. It can be assumed that as fundamental understanding of the etiology and pathogenesis of lymphoid malignancies grows, better diagnostic tools, prognostic markers, preventive, and therapeutic regimens will emerge (Fan, 2003).

Conclusions

The clinical signs of lymphoma in cats vary significantly depending on the anatomical form, without pronounced tissue specificity, and are characterized by signs of single or multiple involvement of systems and organs. The predisposition to lymphoma is highly dependent on the prevalence of certain breeds. In the disease structure, the proportion of mixed-breed cats was 36.1%, Scottish breeds 22.2%, British breeds 19.4%, and Devon Rex 11.1%.

The increase in animal age directly correlates with the incidence of lymphoma in cats with the highest rates found in individuals aged eight to ten years (36.1%) and older than ten years (33.3%). In the absolute majority of cases, alimentary lymphoma was diagnosed in cats (41.6%), with the risk of its development exceeding the likelihood of developing multicentric form by 1.4 times, mediastinal form by 2.5 times, and extranodal form by 3.7 times.

Lymphoma in cats, regardless of the anatomical form, is accompanied by significant ($p < 0.001$) disturbances in general clinical and biochemical blood parameters, indicating the presence of anemia, immunodeficiency, intoxication, and structural abnormalities of organs and tissues.

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