

Pathohistological features of mediastinal lymphoma in domestic cats

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The article covers two clinical cases of domestic cats suffering from a mediastinal form of lymphoma and provides their cytological, immunohistochemical, and pathohistological verification. The lymphoma immunophenotyping method using the B-cell markers CD79a and CD3 was used to identify T-cells. The mediastinal type of lymphoma in cats is usually rarely registered and statistically, the number of cases does not exceed 20%, which is consistent with our observations. Shortness of breath, difficulty with swallowing, lack of appetite, cyanotic mucous membranes, lymphadenomegaly of the mediastinal lymph nodes and effusion in the chest cavity were found in the clinically ill cats. An X-ray examination of the chest cavity revealed an increased contrast in the mediastinal area and displacement of the lungs towards the spine. A complete blood count revealed lymphopenia. Cytological smears of the chest cavity transudates revealed mostly monomorphic lymphoblasts with large rounded hyperchromic nuclei and narrow cytoplasm stained in light blue. The karyoplasm was somewhat granular, the nucleoli were visible, and the mitoses were atypical and numerous. The cytological picture in biopsy samples of mediastinal lymph nodes was characterized by a monomorphic population of lymphoblasts with an eccentrically located nucleus and moderately basophilic karyoplasm. The cell cytoplasm was vacuolated in some places, with presence of atypical mitotic figures. Most of the cells had two nuclei. Diffuse tumoral lesions of the chest cavity tissues, focal tumorous lesions of the lung parenchyma, and lymphadenopathy of the mediastinal lymph nodes were found during the autopsy in the first case. The second clinical case demonstrated the massive lymphadenopathy of the mediastinal lymph nodes. Histologically, a diffuse lesion by a monomorphic population of lymphoblasts was revealed in preparations from the soft tissues of the chest wall. The lymphoblasts' insignificant cytoplasm, with nuclei from round to elliptical shape, infiltrated the chest wall's soft tissues. It was found immunohistochemically that the blast cells showed reactivity to CD79a, and were mostly negative to CD3. This indicates the development of a large diffuse B-cell lymphoma. The immunohistochemical picture of lymph node necropsies from another cat was somewhat similar. However, it was also characterized by lymphoblasts with eccentrically placed nuclei, increased number of cells with mitotic figures, somewhat intensive CD3 antibodies expression (especially in the paracortical area of lymph nodes), and significant CD79a marker expression.

Keywords: cats; lymphoblasts; soft tissues of the chest wall; mediastinal lymph nodes; B-lymphocytes; T-lymphocytes; immunohistochemistry; cytology.

Introduction

Lymphoma (lymphosarcoma) refers to a group of malignant hematological diseases of the lymphoid tissue, which accounts for 90% of all diagnosed neoplasms in cats (Kiselow et al., 2008). The results of monitoring studies and data from animal veterinary practice indicate the prevalence of lymphomas among cats of various ages, most often from 4 months to 19 years (Dom, 1967). However, some authors describe a bimodal disease peak, one which occurs at the age of four years, and another at eight years. It is in young animals up to four years of age that the mediastinum lymphomas are detected (Fabrizio et al., 2014).

There are still discussions in scientific circles regarding the causes of lymphoma in cats, but the viral theory is most often considered. It is believed that two RNA genomic viruses belonging to the retrovirus family provoke the appearance of lymphoma. The first is FeLV, a feline leukemia virus, which accompanies the disease most often (immunosuppressive oncovirus) (Gabor et al., 2001; Louwerens et al., 2005; Vail, 2013; Beatty, 2014; Cristo et al., 2019). The second one is FIV, the feline immunodeficiency virus (lymphotropic lentivirus), which plays an indirect role in tumorigenesis, causing the chronic dysregulation of the immune system and oncogenic pathway activation. As a rule, lymphomas result from neoplastic transformation and subsequent proliferation of lymphocytes in lymphoid organs (Callanan et al., 1996). The disease can develop

in several organs simultaneously or originate from a specific organ with gradual spread to the others. However, it is not entirely correct to consider such spread as metastases.

Depending on anatomical localization, lymphomas are divided into alimentary (abdominal), mediastinal, multicentric, and extranodal. Alimentary lymphoma is one of the most common forms of lymphoma in cats, which, according to statistics, accounts for 32 to 72% of cases and is characterized by local or diffuse damage to the mesenteric lymph nodes and all layers of the stomach and intestine walls (Gabor et al., 1998; Guilermo, 2001; Richter, 2003).

The mediastinal type of lymphoma in cats was registered less frequently and statistically, the number of cases did not exceed 20% (Woldemeskel, 2020). Characteristic multifocal lesions were detected in the thymus, pleura, and mediastinal lymph nodes. This type of lymphoma with a characteristic pleural effusion and a positive reaction to the leukemia virus (FeLV) was diagnosed in young cats between two and four years of age (Seo et al., 2006; Jaroensong et al., 2022).

The multicentric form of lymphoma, which occurs in 20–30% of cases, is characterized by damage to the superficial lymph nodes and possible subsequent damage to the liver and spleen (Keller et al., 2013). At the same time, half of the animals demonstrated positive test results for FeLV antigens. Bone marrow lesions due to multicentric lymphoma were noted in 70% of cases, under correlation of hematological indicators within

control values. Statistically, the extranodal form of lymphoma accounts for 10–15% of cases. First of all, non-lymphoid organs are affected, i.e. kidneys, eyes, nose, central nervous system, and skin. Cats are usually negative for the leukemia virus. In all other cases, 30–50% of animals retain a positive FeLV status (Little et al., 2007; Ota-Kuroki et al., 2014; Silva et al., 2022).

There are several histological classifications of lymphomas in humans, which were also used by veterinary pathologists for some time to evaluate the appearance of neoplasms at the microscopic level. These are the Rappaport and Kiel classification schemes (the updated Kiel classification scheme remains the standard in Europe nowadays). Lymphomas are highly differentiated in animals. However, Hodgkin's lymphoma is virtually undetectable in animals. This is the main difference between human and animal lymphomas. Generally, the issue of histological classification of lymphoid malignant neoplasms in veterinary medicine remains unresolved and is a subject of constant changes and additions.

A histological classification scheme known as the Working Formulation (NCI-WF) was developed by the National Cancer Institute and is used to verify lymphomas in dogs and cats (Valli et al., 2000; Sato et al., 2014). The NCI-WF uses the mitotic index and natural progression rate to classify tumours as low, intermediate, or highly differentiated ones. It is believed that highly differentiated tumours contain large lymphoblasts with wide cytoplasm and low mitotic activity and may refer to B and T cell types. Accordingly, low differentiated tumours have high mitotic activity, clinically rapid progress and, as a rule, are of the B cell type (Carter et al., 1986; Fournel-Fleury et al., 1997).

There is also an updated classification scheme for lymphoid neoplasms, known as the Revised European American Lymphoma system (REAL), but it is not used much for pets. The REAL scheme combines morphology, immunophenotype, and genotype for the classification of lymphoid tumours. It also includes a list of lesions concerning their histogenic differentiation and biological behaviour, but without division into high and low differentiated (Chino et al., 2013; Collette et al., 2016). Immunophenotyping is performed using monoclonal antibodies specific for differentiation antigens expressed by lymphocytes and additional immune cells to identify their lineages. Immunophenotyping is an objective adjunct to the conventional lymphoma assessment, which is based solely on morphology. For this reason, immunohistochemistry (IHC) or immunocytochemistry remains the gold standard for immunophenotyping lymphomas in humans, dogs, and cats. Typical protein markers for the identification of B and T lymphocytes are CD79a and CD3, respectively (Valli et al., 1981; Ferrer et al., 1993; Valli et al., 2000; Sirivisoot et al., 2017).

Our work is aimed at studying pathocytological samples, radiographs, pathoanatomical and pathohistological changes in cats with the mediastinal form of lymphoma with their subsequent immunophenotyping using immunohistochemistry methods.

Materials and methods

During the studies, we followed the general rules of the appropriate GLP laboratory practice (1981), positions of the General Ethical Principles of the Experiments and Animals, approved by I National Congress of Bioethics (Kyiv, 2001). All the experimental part of the study was conducted according to the requirements of the International Principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986), Rules of Studies using Experimental Animals, approved by the order of the Ministry of Healthcare No. 281 as of November, 1, 2000, "On Measures for Further Improvement of Organization Forms of Studies using Experimental Animals and the corresponding Law of Ukraine "On Protection of Animals against Abuse (No. 3447-IV as of 21.02.2006, Kyiv).

This retrospective study was conducted during 2019–2022 on cats at the veterinary clinic Vetpraktik, located in Lviv, 5 Panch Str. More than twenty biopsy samples were studied and ten pathological autopsies were performed. Two cats were diagnosed with mediastinal lymphoma, the others with abdominal and extranodal lymphoma. Anamnestic data from the owners, clinical signs of the disease, results of hematological and biochemical studies, radiographs, results of fine-needle aspiration biopsy were recorded in each case separately. Autopsy and pathohistological

examination were performed in the laboratory of the Department of Normal and Pathological Morphology and Forensic Veterinary Medicine of Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies. X-ray studies were carried out using the MAXIVET 400 HF digital device.

Cytopathological samples were taken directly from neoplasms using a fine-needle biopsy under the control of ultrasound examination. At least three cytological smears were made for cytopathological examination, dried, fixed in methanol, stained according to the Romanovsky-Giemsa method, and examined under a Leica DM-2500 light microscope. Based on generally accepted cytological criteria, the lymphoma diagnosis was made. With the permission of the animals' owners, an autopsy was performed after the death of the cats with the selection of tissues for histopathological examination. Fragments of the affected organs were fixed in a 10% aqueous solution of neutral formalin, washed, dehydrated in an ascending series of alcohols, followed by embedding in paraffin according to the generally accepted method (Merkulov, 1969). Histosections with a 7 µm thickness were made from paraffin blocks on an MC-2 sledge microtome. For light microscopy, deparaffinized sections were stained with Mayer's hematoxylin and eosin. Light microscopy and photomicrography of the obtained tissue preparations were carried out using a Leica DM-2500 microscope and a Leica DFC 450C camera. 7-µm thick sections were immunophenotypically classified using CD3 and CD79a markers to identify T and B cells, respectively. A mediastinal lymph node with no deviations from the norm from a clinically healthy cat that died from a traumatic injury was used as a control specimen. Immunophenotyping was performed at the Department of Pathological Anatomy, Faculty of Veterinary Medicine (University of Warmia and Mazury in Olsztyn, Poland).

Results

Twenty cats of various ages with suspected lymphoma were observed at the clinic during 2019–2022. Two of them were purebred sterilized cats with mediastinal lymphoma, aged three and six years. From the anamnestic data, it is known that the cats occasionally showed signs of difficulty with swallowing, shortness of breath, cyanotic and icteric mucous membranes, lack of appetite, lymphadenomegaly, and cachexia. According to the protocol, the additional tests were performed: a general blood test, X-ray diagnostics of the chest cavity organs, and a fine-needle biopsy of both the mediastinal lymph nodes' tissues and the chest cavity contents. Express blood tests were carried out to detect the leukemia virus. One cat with mediastinal lymphoma tested positive for FeLV. Due to the serious condition and the late application for help to the veterinary clinic, the animals were incurable and soon died of natural causes before the treatment started.

The smears obtained from chest cavity exudate by the method of the fine-needle biopsy under ultrasound control and stained according to Romanovsky-Giemsa method, revealed that the bulk of the cell pool consisted of various lymphoblasts (Fig. 1a, b). It was possible to observe pronounced cellular anisocytosis and anisokaryosis, with 2–3 visible atypical mitotic figures. In smears from lymph nodes, most cells were monomorphic with a narrow, slightly vacuolated cytoplasm, moderately basophilic nuclei, mostly with two nucleoli; cellular anisocytosis and anisokaryosis were not expressed (Fig. 2a, b, c, d).

X-ray examination of the chest cavity revealed significant areas with increased X-ray contrast (Fig. 3a, b) and pleural effusion. The lungs in cats were pushed to the spine, which explained their shortness of breath. Due to the massive compacted area, the heart outlines were practically not visible.

In the first case, diffuse tumour growth in the chest wall's soft tissues, and focal lesions of the lung parenchyma and mediastinal lymph nodes were found during the pathological autopsy. In the second case, a diffuse lesion of the mediastinal lymph nodes was detected. A red transudate was present in the chest cavity of both cats. Neoplasms on the costal pleura were light grey to white in colour, dense in consistency, moderately wet, and smooth on cross-section (Fig. 4a). Neoplasms of the mediastinal lymph nodes formed massive rounded, bumpy, and light pink compactations of different sizes (Fig. 4b). In both cases described above, a multino-

dular shapeless pale pink structure of dense consistency was found, which occupied most of the chest cavity, displacing the lungs to the spine.

Diffuse infiltrates of monomorphic lymphoblastic cells with small cytoplasm and hyperchromic nuclei from round to elliptical shapes were localized between myocytes. They are visible on histological preparations of the chest wall's soft tissues (Fig. 5a, b). Immunohistochemical examination showed the tumour cells showed reactivity to the CD79a marker and were mostly negative to CD3, which indicated a B-cell type of lymphoma (Fig. 5c, d). The expression of CD3 detected in isolated cellular elements indicates the presence of cytotoxic T-lymphocytes, which are

involved in the induction of a specific immune response and the production of cytokines that affect all links of the inflammatory process.

In addition to massive lymphoblastic infiltration of the sternum soft tissues, damage to the mediastinal lymph nodes was noted, in which a significant marginal sinus expansion, stasis, diffuse infiltration by cortical substance, and lymphoid nodes lymphoblasts was established (Fig. 6a, b). Interfollicular spaces are also filled with a monomorphic population of lymphocytes. Immunohistochemically, there was a positive reactivity of cells to CD79a marker both in the area of the marginal sinus and in the lymphoid nodules' center, which indicated the B-cell type of lymphoma (Fig. 6).

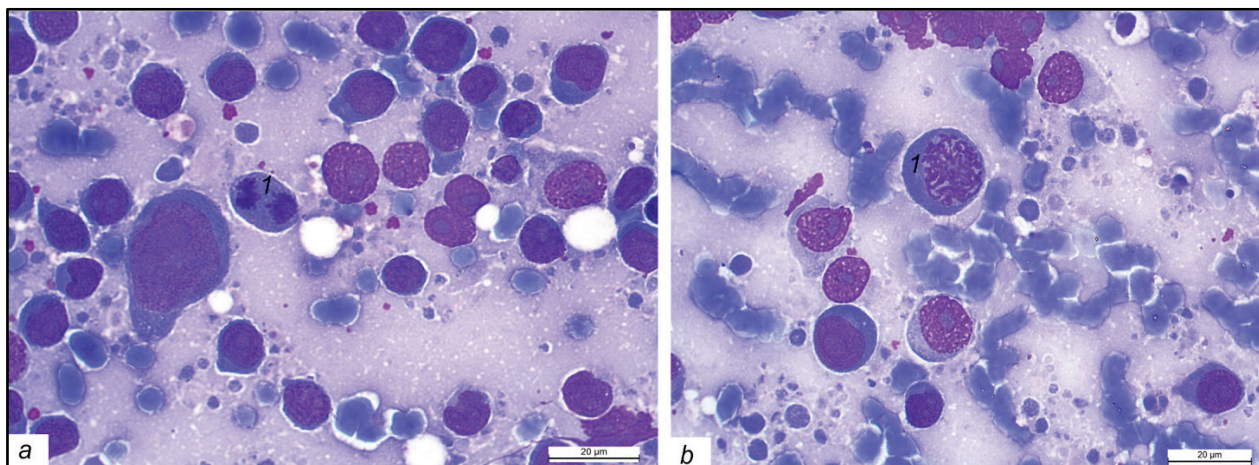


Fig. 1. Cytological samples of transudate from a cat's thoracic cavity: mediastinal form of lymphoma; *a* – the population of lymphoblasts with granular karyoplasm and narrow cytoplasm; *b* – atypical mitoses (1); Romanovsky-Giemsa

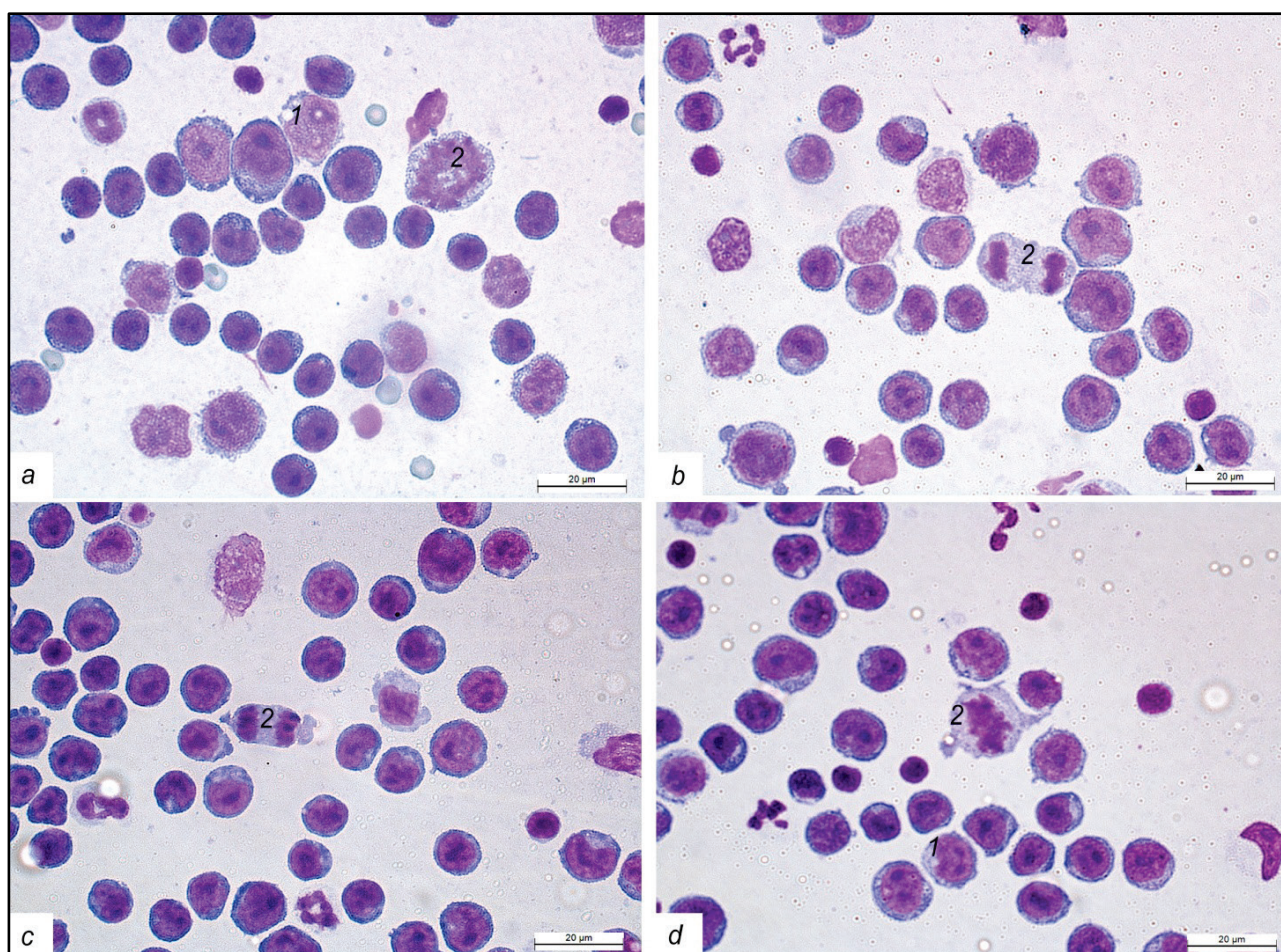


Fig. 2. Cytological biopsy samples from a cat's lymph nodes: mediastinal form of lymphoma; *a, b* – a monomorphic population of lymphoblasts with cytoplasmic vacuolization and significant nuclear hyperchromicity (1); *c, d* – atypical mitotic figures (2); Romanovsky-Giemsa

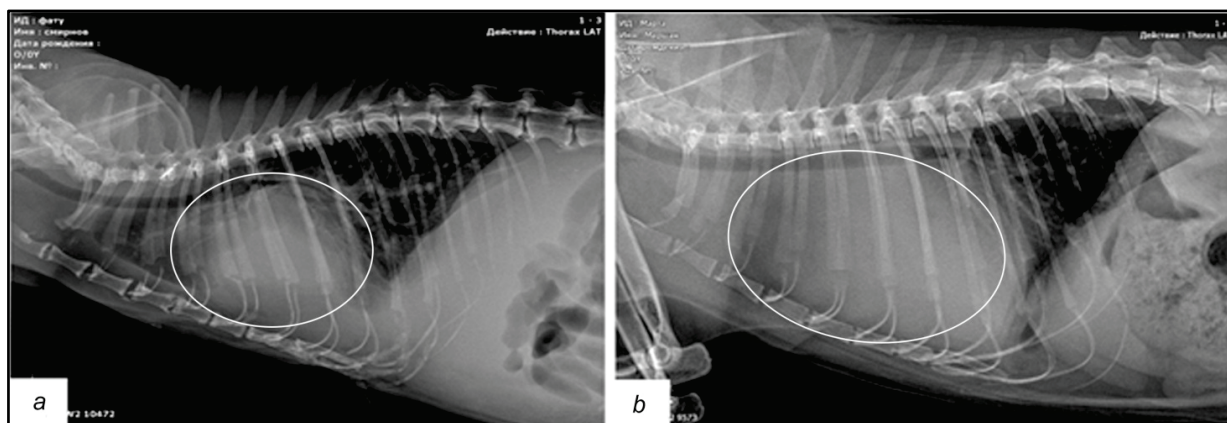


Fig. 3. X-ray of a cat's chest in the lateral position: *a* – increased X-ray contrast of soft tissues in the sternum area; *b* – the lungs are pressed to the spine

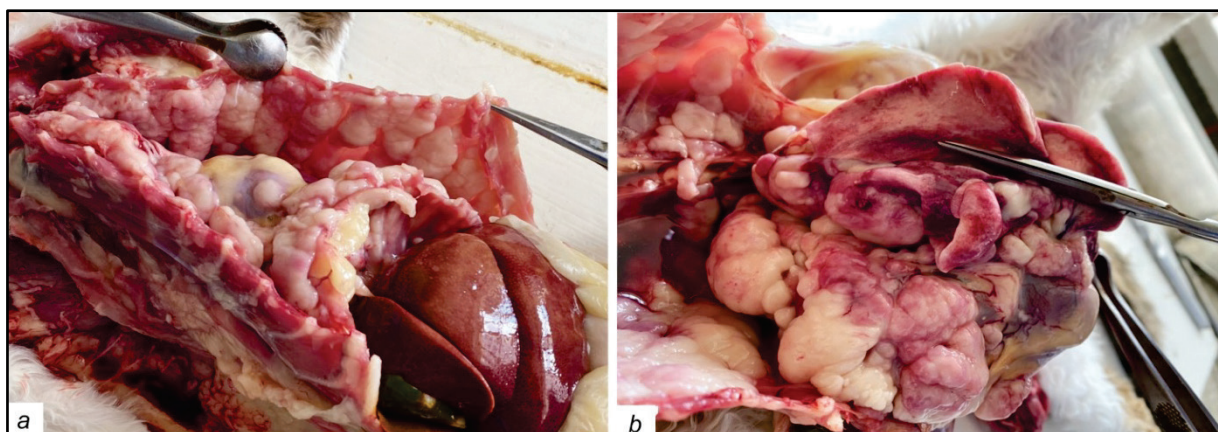


Fig. 4. Mediastinal form of lymphoma: *a* – diffuse lesion of the chest wall and diaphragm in a cat; *b* – a massive neoplasm in the mediastinal lymph nodes' area

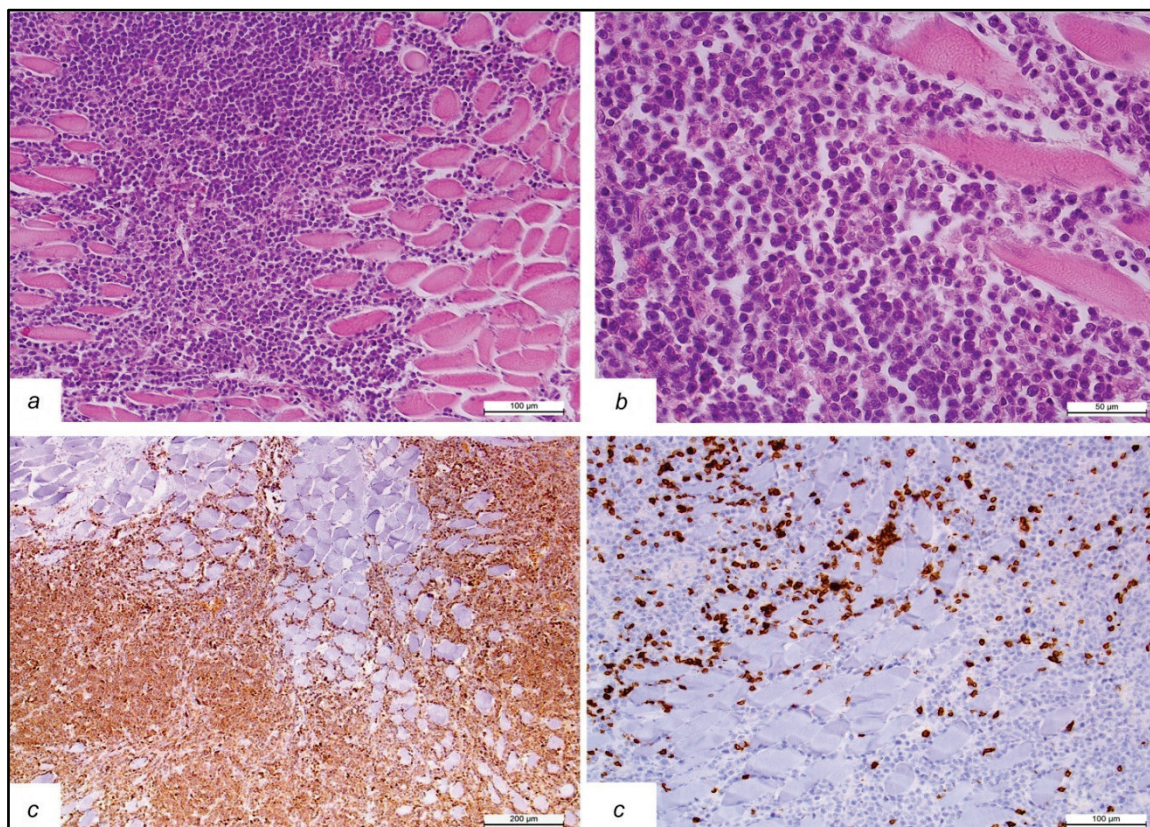


Fig. 5. Mediastinal form of lymphoma: *a, b* – massive infiltration of the chest wall muscles by lymphoblasts; H&E; *c* – immunohistochemical staining with CD79a marker; lymphoblastic cells with intense cytoplasmic expression of CD79a; *d* – immunohistochemical staining with CD3 marker; single CD3+ T-lymphocytes are noted among a large number of cells; IHC

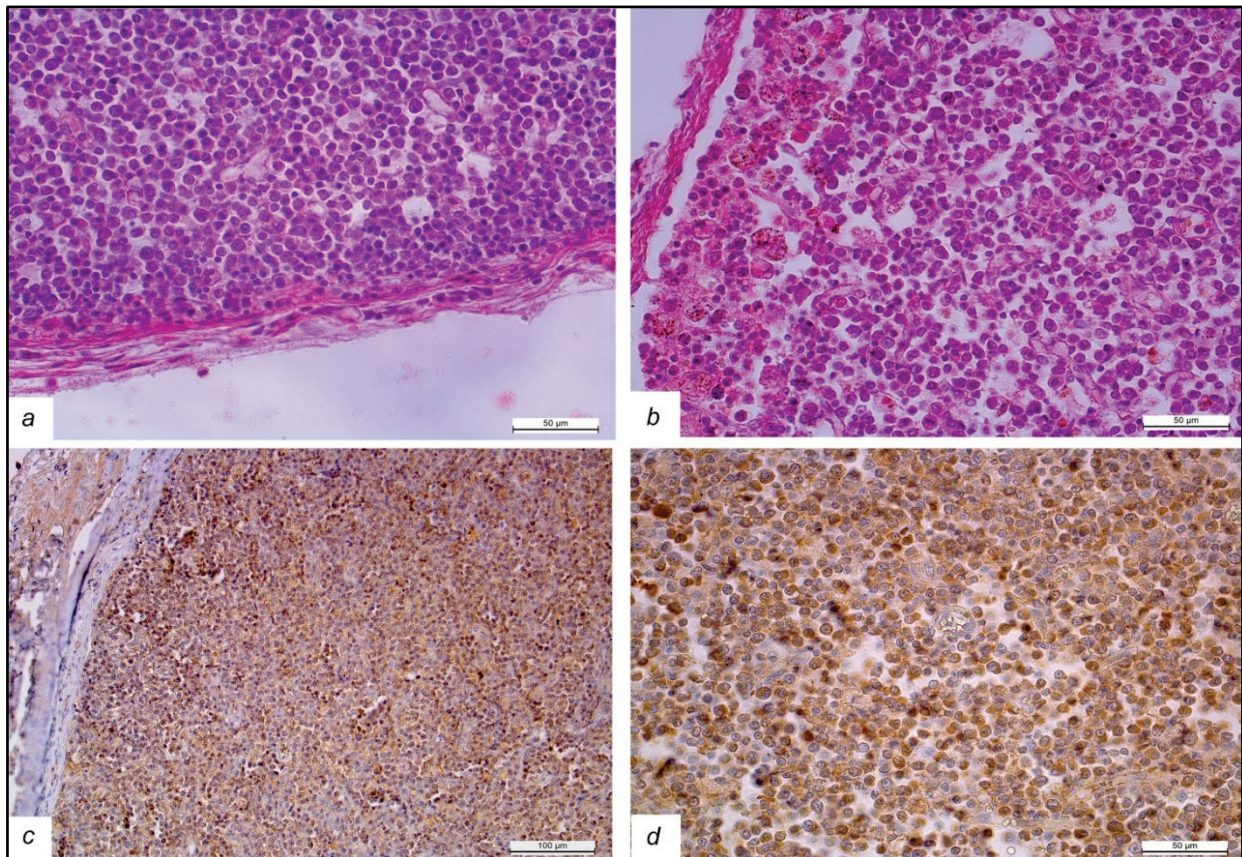


Fig. 6. Mediastinal form of lymphoma – lymph node: *a* – diffuse B-cell infiltration, cell nuclei are large, round with a prominent, single, and central nucleolus; *b* – marginal sinus enlargement; H&E; *c*, *d* – immunohistochemical staining with CD79a marker, the positive result of CD79a antibody labeling of neoplastic B-cells of the marginal sinus and lymphoid nodule; IHC

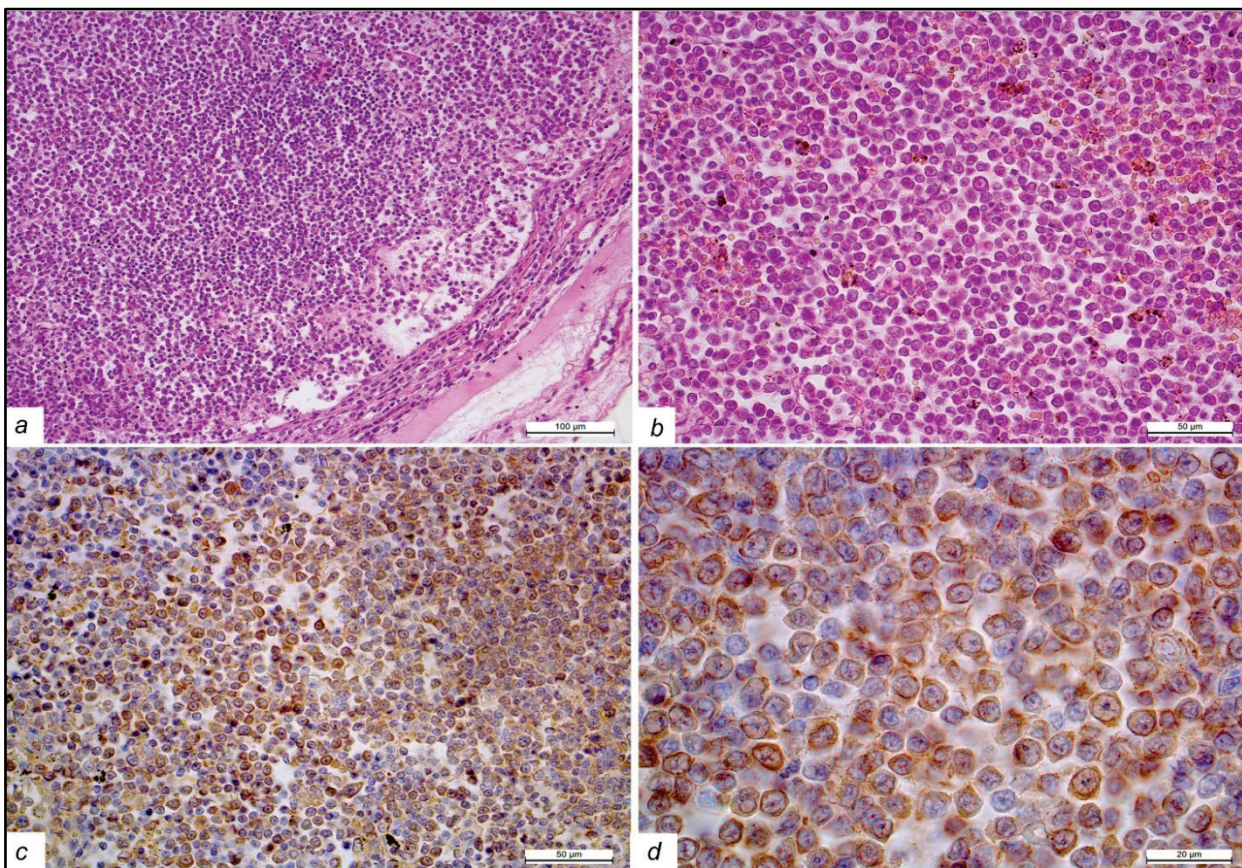


Fig. 7. Mediastinal form of lymphoma – lymph node; *a*, *b* – lymphoblasts with hyperchromic nuclei are infiltratively located both in the cortical and brain areas; H&E; *c*, *d* – immunohistochemical staining with CD79a marker, neoplastic cells showed intense positive immunostaining of lymphoid nodules with CD79a antibody; IHC

The histological picture was generally similar in the mediastinal lymph nodes of the other animal. Monomorphic lymphoblasts were infiltratively located both in the cortical substance and the lymphoid nodules, the blood vessels were dilated and filled with erythrocytes (Fig. 7a, b). The nuclei of such cells were hyperchromic with little cytoplasm. Cellular anisocytosis was not pronounced. Immunohistochemically, the tumour cells had a marked reactivity to CD79a marker (Fig. 7c, d).

Discussion

According to some authors, lymphoma has a bimodal clinical picture. This is confirmed by the research in the first group of two-year-old cats with a positive reaction to FeLV. Apart from the cats' mediastinal lymph nodes, the thymus, submandibular lymph nodes, and respiratory organs with pleural sweating in the chest cavity are sometimes affected. The second group includes older cats, aged from 6 to 12 years. Mainly, they demonstrate a negative reaction to FeLV, combined most frequently with the digestive tract lymphoma of the alimentary type.

Despite the decreasing trend in FeLV disease in cats worldwide, the prevalence of lymphomas, on the contrary, is constantly increasing. Etiological factors are currently unknown. There is a theory that some genetic factors contribute to the appearance of lymphomas in cats. Siamese cats and related breeds have a much higher risk of this disease (Malik et al., 2003; Krick et al., 2008; Burkhard & Bienzle, 2013; Broman & Miller, 2016). The breed features, the absence of retroviruses, the early disease onset (under the age of 2 years) and the typical clinical picture indicate a hereditary form of lymphoma in Siamese breeds.

Diagnostics and treatment of the mediastinal form of lymphoma in cats remain one of the most challenging issues in modern veterinary oncology. It is caused by the probable tendency of lymphoma growth in recent years, the difficulty of their timely detection, the late start of therapy, and, as a result, the negative prognosis for sick animals. The average age of cats described in our study coincided with the results obtained by other scientists (Gabor et al., 1999; Valli et al., 2000; Gabor et al., 2001; Collette et al., 2016). Most researchers described mediastinal lymphoma along with the inflammatory changes in the respiratory organs.

The two cases of mediastinal lymphoma described above were registered in cats aged three and six years with the signs characteristic for the cats of the first group of the bimodal clinical picture. They included shortness of breath, difficulty with swallowing, anemia of the mucous membranes and icterus, pleural effusion, partial dysphagia, enlarged lymph nodes, and general cachexia. An autopsy revealed a massive neoplasm on the soft tissues of the lateral chest wall and damaged mediastinal lymph nodes. Studies of cytopathological samples from transudate and mediastinal lymph node biopsies revealed monomorphic neoplastic lymphoid cells with round hyperchromic nuclei and small cytoplasm. Immunohistochemically, the neoplastic cells in one cat with soft tissue lesions of the chest wall and mediastinal lymph nodes were mostly positive for CD79a and slightly positive for CD3. However, the B cell phenotype predominated.

Conclusion

We diagnosed a large mediastinal B-cell lymphoma (DLBCL) based on the results of a complex pathomorphological examination.

The authors declare that they have no potential conflict of interest concerning the authorship or publication of this article.

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