

Clinical and pathomorphological characteristics of spontaneous neoplasia of the dairy gland in dogs

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The article deals with the data of clinical examination of 127 females with neoplasia of the mammary gland (MG) and the results of cytological examination of tumors at the preoperative stage and their pathologist verification after mastectomy. In the primary examination of animals, clinical signs characteristic of breast tumors are found in 102 (80.3%) dogs. According to the criteria of the international clinical TNM classification, in 44 (43.14%) females, I stage of development of the tumor process was established, in 25 (24.51%) - II, in 29 (28.43%) - III and 4 (3.92%) - IV stage of tumors. In 25 (19.7%) of 127 dogs, the signs of neoplasia were fuzzy since symptoms of fibrocystic disease were at the forefront. According to the results of the histological searches, 88 or 69.3% of the animals were diagnosed with neoplasia of malignant nature, 14 or 11.02% were benign tumors, and in 25 or 19.7% of cases, dysplasia was diagnosed. It was also established that 74 (84.1%) episodes of MG tumors were epithelial, and 28 (15.9%) of other origins. Among malignant neoplasms, the most commonly reported were simple carcinoma, which were 27 (21.26%), complex carcinoma - 26 (20.47%), non-infiltrative carcinoma in situ 18 (14.17%), and rarely was found carcinomas of particular types, namely 3 (2.36%), sarcoma - 10 (7.87%), carcinosarcoma - 4 (3.15%). Benign tumors are represented by fibroadenoma (7.87%) and simple adenoma (3.15%). For localization of the primary lesion, in 53 (60.2%) of the studied tumors, duct cancer was recorded; in 21 (23.9%) cases, the primary cells were detected in the lobes and, respectively, 14 (15.9%) lesions captured both the lobules and the ducts. The results of retrospective searches of dogs diagnosed with fibrocystic disease have shown that in over 40% of these animals, the proliferative form of mastopathy has been verified, as well as signs of its transformation and microfocus tumor growth, which may indicate the direct involvement of this disease in carcinogenesis. According to the results of a comparative analysis of clinical stages and histological types of spontaneous breast tumors in females, it has been found that the magnitude of the tumor and the degree of its malignancy are interrelated, as a tendency is observed, in which, along with the growth of the T index, which according to the clinical TNM classification of the tumor reflects its size, the number of cases of neoplastic neoplasms that are malignant is increasing.

Keywords: dogs, neoplasia of the mammary gland, TNM classification of tumors, cytological and histological research methods.

Introduction

It is well known that among cancers in dogs, tumors and tumor-like lesions of the mammary gland (MG) in females occupy not only the top place but also are characterized by a considerable variety of pathologies regarding the localization, stage, and nature of the pathological process, the clinical manifestation of the disease (Mac Ewen & Withrow, 1996; Mouser et al., 2010). Under such conditions, to clarify the nature of neoplasia, the establishment of an accurate diagnosis and nosological verification of cancer requires a comprehensive examination of animals and, respectively, carrying out of several clinical, instrumental, laboratory, and in some cases and particular searches (Gama et al., 2008; Rivera & von Euler, 2011).

However, in determining the final diagnosis, the priority belongs to pathomorphological research, since the malignant tumor is definitively established, which is confirmed by the cytological or histological method of research, and the formulated based on this pathomorphological diagnosis reflects the histological type of neoplasm and the degree of its malignancy (Badowska-Kozakiewicz & Milacka, 2011; Goldschmidt et al., 2011). It should be noted that today the conduct of retrospective searches of neoplasia, their clinical manifestations, cytological and histological characteristics, as well as other aspects of the verification of tumors are significant both for practicing doctors, in particular, for choosing the tactics of therapeutic measures, forecasting the course of the disease (Yamagami et al., 1996; Santos et al., 2013), as well as for the monitoring and statistics of oncological diseases and the exchange of information between specialists working in the field of veterinary oncology (Webster et al., 2011; Matos et al., 2012; Mysak et al., 2018; Gutyj et al., 2018).

The purpose of the research was to establish the clinical and pathomorphological characteristics of spontaneous tumors of the mammary gland of dogs at the stage of preoperative examination and compare the findings with the results of postoperative histological verification of excisional material.

Materials and Methods

The research was carried out at the clinic of small animals of the Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, during 2006-2016. One hundred twenty-seven females of different breeds aged 5-16 years with single and multiple tumor lesions of the mammary gland (MG) were the research object. During the initial examination of the sick animal, the classification of tumors was carried out according to the international clinical TNM systematics of L. N. Owen (1980). For morphological verification of neoplasia at the stage of preoperative examination of dogs, cytological searches were performed. The material (*in this case*) was smeared with biopsy punctate smears printed on the surface of tumors, secretions from the nipple of the MG, and pleural fluid. Punctic biopsy of tumor-like MG and regional lymph nodes was performed under the control of sonography to use a half-automatic needle guillotine of type SpringCut 14G. The smears were dried in air, fixed with methyl alcohol for 5 minutes, painted with Romanovskyj-Gimz, and studied under a microscope using an immersion system. The cytological diagnosis of MG disease was based on the study of the background and structural features that reflected the location between the cells, the state of cells themselves and their components, and their changes concerning organ analogs in the normal. In the cytograms, the focus was on the size of the cells and nuclei, their placement, the number of nuclei, the nuclear-cytoplasmic ratio, chromatin structure, the number and nature of the mitoses. These morphological indicators were used to determine the nature of the process (benign, malignant) and evaluate the degree of differentiation of cells.

The results of pathomorphological neoplasm verification established the final diagnosis. One hundred sixty-eight tumors removed during mastectomy in 127 females were the material for histological examination. From each tumor, 3-4 samples were taken. The material was fixed in a 10% neutral formalin solution for histological preparation, conducted through spirits of increasing concentration, and poured in paraffin blocks. Made cuttings were stained with hematoxylin and eosin and studied using a binocular microscope MBI-1 with an increase of 400-800 times. In this case, the histological type and degree of malignancy of the tumors, the localization of the primary lesion (ducts or lobes) were determined, based on which the metastatic properties of the tumors under study and their ability to generalize were assessed. Pathomorphological searches were carried out at the Department of Normal and Pathological Morphology and Forensic Veterinary Medicine of the Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv. The pathologic morphological verification of excisional material was carried out following the International Histological Classification of Breast Cancer in Dogs and Cats (Misdorp et al., 1999).

Results and discussion

At the initial examination, 127 females who entered the clinic with lesions of MG, characterizing clinical signs of neoplasia, were found in 102 (80.3%) of animals. According to the criteria of clinical TNM, the classification of tumors in 44 (43,14%) of these dogs has established the I stage of development of the tumor process (T1bN0M0, T1aN1aM0), in 25 (24.51%) - II (T1bN1aM0, T1bN1bM0, T1b, BN1aM0, T1b, BN16M0, T2aN0M0, T26N0M0, T26N1aM0, T26, BN1aM0), in 29 (28.43%) - III (T1b, in the N2bM0, T2b, BN16M0, T3aN1aM0, T36N1M0, T36, BN1aM0, T36, BN16M0) and 4 (3.92%) dogs - IV (T3b, in BN1bM1, T3b, in BN2bM1) the stage of tumors. In 25 (19.7%) of 127 dogs, the signs of tumors were not visualized visually since the symptoms of fibrocystic disease or inflammatory process in the MG were at the forefront.

It was established that neoplastic lesions were most often localized in the inguinal (41.07%) and caudal abdominal (32.73%) MG packages, less frequently in the cranial abdomen - 16.65% and caudal breast - 6.54% and only 2.97% of the cases was the cranial chest of MG.

According to the results of studying the dynamics of tumor growth, namely, the rate of development and pathogenetic changes, since the appearance of the primary symptoms of the disease were established, in 29 (22.8%) animals, the rate of development of neoplasia of MG was high speed since during 52.7 ± 1.85 days the tumors were doubled in size (6-9 weeks from small nodes or densities, tumors were formed in the diameter of 5-10 cm), which is evidence of effective aggressiveness of tumor growth. In 47 (37.0%) females, the doubling of the magnitude of the primary tumor reached, on average, six months (172.1 ± 17.6 days), and in 51 (40.2%) animals, the period of development of tumors lasted for two to five years.

At the stage of the preoperative examination of dogs with tumors, tumor-like formation, or MG seals, 214 samples of material were selected and subjected to cytological examination: in 131 cases, puncture biopsy was applied, 56 dogs were examined for nipple excretion, 5 for pelvic exudates, and 22 for smears from the tumor surface.

As it was shown the result of a cytological study conducted in 127 females for neoplasia of the mammary gland and its analysis, the diagnostic efficiency was 96.07% (Table 1).

The obtained results allowed not only to evaluate the diagnostic ability of cytological research in various ways but also to identify the inflammatory, dystrophic, cystic, and tumor processes and determine the nosological structure of MG disease.

According to the international TNM systematics, each investigated tumor was evaluated according to the criteria of two complementary classifications: clinical (cTNM) classification is based on clinical and other research methods conducted before treatment, whereas the basis for the pathogistological (pTNM) classification is the data obtained during the surgical intervention and the results of the histological examination of the removed tumor.

Table 1. Results of cytological examination of neoplasia of MG in females (n = 127)

The nature of mammary gland pathology	Results of cytological research			
	Those that confirm the diagnosis		doubtful	
	number of animals	%	number of animals	%
Benign tumors	14	11.02	-	-
incl. complicated: - mastopathy	4	3.14	-	-
- inflammation	-	-	-	-
Fibrosopic mastopathy	19	14.96	-	-
Inflammatory process	3	2.36	3	2.36
Malignant tumors,	86	67.71	2	1.57
incl. complicated: - mastopathy	9	7.08	-	-
- inflammation	14	11.02	-	-
Total	122	96.07	5	3.93

It should be noted that the data established during the execution of the mastectomy are essential both for confirming or refuting the results of the preoperative clinical examination, and for the interpretation of the pathologist diagnosis, as in the process of surgical intervention, a visual refinement of the topography of the primary focus and the spread of the tumor process to adjacent tissues were performed, the breast macrostructure was evaluated in comparison with the anatomical norm and the angiogenesis of both the tumor itself and the surrounding tissues. In addition, the results of the morphological examination of each extracted tumor are of great importance for the interpretation of the pathologist's diagnosis, which gives an opportunity to assess in detail the native value (size) of the tumor, its shape, consistency, color, tissue structure, the presence of cysts, tissue decay sites or necrotic content cavity, as well as determine the sites for selecting the material for histological examination.

Postoperative pathologic verification of neoplasia was conducted following the International Histological Classification of MG Tumors in Dogs and Cats (1999), according to which the tumors were identified by tissue origin and histological type. The generalized results of histological studies of tumor material are presented in Table 2.

According to the results of the histological study (Table 2), 88 or 69.30% of the animals were diagnosed with neoplasia of malignant nature, 14 or 11.02% were benign tumors, and 25 or 19.70% of cases, dysplasia was diagnosed. It is also established that in 74 (84.1%) MG tumors were epithelial and, respectively, 28 (15.9%) of other origins. According to the histological structure, malignant neoplasms were distributed as follows: noninfiltrative carcinoma in situ - 18 (14.17%), tumors, complex carcinoma - 26 (20.47%), simple carcinoma - 27 (21.26%), carcinoma of special types 3 (2.36%), sarcoma - 10 (7.87%), carcinosarcoma - 4 (3.15%). Benign tumors are represented mainly by fibroadenoma (7.87%) and simple adenoma (3.15%).

Table 2. Pathomorphological characteristics of MG neoplasia in females (n = 127)

Origin	Code of tumors	Histologic type of tumor	Number of cases
Epithelial tumors	1.1.	non-infiltrative (in situ) carcinoma,	18
	1.2.	complex carcinoma,	26
	1.3.	simple carcinoma, including:	27
	1.3.1.	tubular (tubular papillary)	16
	1.3.2.	solid	9
	1.3.3.	anplastica	2
	1.4.	special type carcinoma	3
Mesenchymal tumors	1.5	sarcoma, including:	10
	1.5.1	fibrosarcoma	8
	1.5.2	chondrosarcoma	2
Mixed	1.6	carcinosarcoma	4
		Together	88
Benign tumors	2.1.	simple adenoma	4
	2.2.	fibroadenoma	10
	4.	dysplasia	25
		Together	39
	Total		127

The analysis of the results of histological studies has shown that carcinogenesis of MG tumors can be manifested by varying degrees of malignancy; therefore, for the formulation of pathomorphological diagnosis, it is important to determine the specific types of cells and the localization of the primary cell of the tumor process. Therefore, in over 65% of the studied tumors of MG,

heterogeneity of the tumor structure was detected due to the combination of several types of tumors or microfocus tumor growth together with hyperplasia of varying degrees of severity. In a detailed study of the histostructure of neoplasia, it was also noted that in the field of view, in more than half of the histopreparations, structural changes that are characteristic of the proliferative form of mastopathy have been identified. Therefore, while concurrently detecting several forms of tumor growth, the final diagnosis was established based on the predominant component and type of specific tumor cells, and only in rare cases, the tumors were verified as mixed. In particular, it has been established that, despite the considerable variety of histological types, most of the malignant tumors of MG could be attributed to adenocarcinoma. It was found that tubulin (n = 10), tubular papillary (n = 6), solid (n = 9), and rarely anaplastic (n = 2) carcinomas were among the simple types of carcinoma. Among other carcinomas, carcinomas have been spotted in situ, squamous cell carcinoma, and cryogenic cancer, as well as carcinomas and sarcomas with chondroid and spindle cell metaplasia.

Results of localization of the primary cells of the tumor process have shown that in 53 cases, or 60.2% of the tumors under investigation, duct cancer was recorded; rarely the primary cells were found in the lobes, which were 21 (23.9%) cases and, accordingly, 14 (15.9%) lesions captured both lobes and ducts. It has also been established that in most episodes, both ductal and mixed wounds were accompanied by an infiltration type of tumor growth, a large number of figures of mitotic cell division, and metaplasia, which is a fact of a high degree of malignancy of tumors.

Comparing the data of the preoperative clinical classification of tumors and, accordingly, the results of the histological examination of the exciting material (Table 3) was found that among tumors of the I stage, 22.7% of cases benign was verified, and 77.3% - malignant tumors. The histologic type of the latter is represented mainly by in situ non-infiltrative carcinoma and carcinomas with a low degree of malignancy.

Table 3. Comparative analysis of clinical stage and histological types of spontaneous breast tumors of females (n = 102)

Histological type	Dogs number	Clinical stage of tumors (by TNM classification)			
		I	II	III	IV
Non-infiltrative carcinoma in situ	18	16	2	-	-
Complicated carcinoma,	26	8	12	6	-
including - low-differentiated	2	-	-	2	-
- moderately differentiated	21	5	12	4	-
- highly differentiated	3	3	-	-	-
Simple carcinoma	27	10	6	10	1
including - low-differentiated	7	-	1	5	1
- moderately differentiated	16	7	5	4	-
- highly differentiated	4	3	-	1	-
Carcinoma of special types	3	-	-	3	-
Sarcoma (fibrosarcoma, chondrosarcoma)	10	-	1	7	2
Carcinosarcoma	4	-	1	2	1
Fibroadenoma	10	7	2	1	
Simple adenoma	4	3	1		
Total	102	44	25	29	4

Among the neoplasias of the 2nd grade, benign tumors made up 12.0% and, accordingly, malignant ones - 88%. By histological type, such tumors are quite diverse, since in addition to tumors of epithelial origin, most of which are complex and, to a lesser extent, simple carcinomas, in two cases, were identified as sarcoma and, accordingly, carcinosarcoma.

According to the histological examination of tumors at the third stage of development, 96.6% of episodes were detected for their malignant nature. The histological type of such tumors is most often represented by simple and less complex carcinomas of a high and moderate degree of malignancy, carcinoma of special types (squamous cell carcinoma and cryopreservation), as well as sarcoma and carcinosarcoma.

The analysis of the data in Table 3 indicates that the magnitude (size) of the tumor and the degree of its malignancy are to some extent interrelated, in particular, there is a tendency in which, along with the growth of the T index, which according to the clinical TNM classification of the tumor reflects its size, and the number of cases of neoplastic neoplasms that are malignant is increasing. It should be noted that an important indicator in predicting the oncological disease is the time during which tumors double their magnitude. This is confirmed by the fact that sarcomas and anaplastic and edema-infiltrative carcinomas are the largest in the studied tumors of MG, which by their size considerably exceed the size of other tumors of stages I and II ($p < 0,001$) and tumors of the third stage ($p < 0,1$), and the time during which these neoplasias doubled their magnitude reaches 52.7 ± 1.85 days. Therefore, determining the size of the tumor, along with determining the rate of growth (the time of doubling the mass of the tumor) and the depth of germination of the tumor in the surrounding tissue, can be considered as one of the clinical parameters that have a prognostic value at the stage of the preliminary examination of tumorous animal carriers.

In the initial survey, 127 females who entered the clinic with lesions of MG, in 25 (19.7%) dogs, the signs of tumors were not visualized rarely; in 19 animals, the symptoms of fibrocystic disease, and 6 were mastitis. According to the results of a retrospective search, 19 dogs diagnosed with fibro-cyst mastopathy in 15 animals diagnosed with dysplasia were histologically confirmed. In this case, in 7 cases, ectasia of ducts and cysts (non-proliferative type of fibrous cystic disease) and 8-lobed

hyperplasia and adenoses were detected proliferative forms of mastopathy; one animal was verified by fibroadenoma. At the same time, in the three animals, dysplasia was unclassified since the complexity of their differentiation was associated with the discovery of signs of typical and atypical lobular hyperplasia, which under certain conditions can be considered a sign of microfocus tumor growth. In this, our data are consistent with the results of searches by several authors (Potockyj & Shestyayeva, 2004; Karpetskaya, 2007; Shestyajeva, 2011), which refer with fibro-cystic disease to pretumor processes.

Conclusion

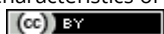
Consequently, the establishment of the proliferative form of mastopathy and the signs of its transformation, which were found in most animals with fibro-cystic mastopathy, may indicate a direct involvement of this disease in carcinogenesis.

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