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Review articles

Canine mastopathy (Overview)

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Abstract. The etiological factors, pathogenesis and clinical and pathomorphological features of mastitis in dogs remain poorly understood, due to isolated, multidirectional studies on a small number of animals. Fibrocystic disease is diagnosed in different species of animals – small domestic, productive and laboratory animals. The clinical signs are not pathognomonic and an atypical course of the disease is possible. The potential role of mastopathy in the development of cancer has been proven, but the pathogenesis of functional dysplasia of mammary tissue, and the internal and external factors that may initiate further neoplastic transformation, remain poorly understood. Mastopathy in bitches is widespread and accounts for 8 to 30% of benign mammary gland neoplasms. Susceptibility varies considerably according to the distribution of breeds in the region. Compared to neoplasms (where the highest incidence is in animals over 7 years of age), mastitis peaks in 5-6-year-old dogs. A hormonal imbalance has been shown to be a direct cause of fibrocystic disease in bitches, and this has been experimentally confirmed in rats. The prognostic significance of estrogen and progesterone receptor expression was clarified. The importance of chronic inflammation in the pathogenesis of fibrocystic disease was shown. A high risk of mastopathy in overweight bitches has been established. Diabetes is a potential risk factor for fibrocystic disease, but further research is needed to clarify the patterns. The prospect for further research is to identify prognostic factors and key biological mechanisms to predict the course of the disease and to develop pathogenetically sound treatment protocols.

Keywords: dogs; cystic fibrosis; prognostic markers; obesity; hormonal imbalance

Мастопатія у собак (оглядова інформація)

Анотація. Етіологічні фактори, патогенез та клініко-патоморфологічні особливості мастопатії у собак залишаються недостатньо вивченими, що спричинено поодинокими, розрізненими за спрямуванням дослідженнями на незначній кількості тварин. Фіброзно-кістозна хвороба діагностована у різних видів тварин – дрібних домашніх, продуктивних та лабораторних. Клінічні ознаки не патогномонічні, можливий не типовий перебіг захворювання. Доведено потенційну роль мастопатії у розвитку раку, але патогенез дисплазії функціональної тканини молочної залози, а також внутрішні і зовнішні чинники, які ініціюють подальшу неоплазійну трансформацію залишаються недостатньо вивченим. Мастопатії у сук мають широке розповсюдження, складають в структурі доброякісних неоплазій молочної залози від 8 до 30 %. Породна сприйнятливість суттєво коливається, залежно від поширення порід в регіоні. Порівняно із новотвореннями (максимальна реєстрація характерна тварин, старших 7 років) пік захворювання реєструється в 5–6-річних собак. Доведено, що безпосередньою причиною розвитку фіброзно-кістозної хвороби у сук є гормональний дисбаланс, що експериментально підтверджено у дослідах на щурах. З'ясовано прогностичне значення експресії рецепторів естрогену і прогестерону. Показано важливе значення в патогенезі фіброзно-кістозної хвороби хронічного запалення. Встановлено високий ризик захворювання на мастопатію у сук, які мають надлишкову масу тіла. Потенційною загрозою розвитку фіброзно-кістозної хвороби є цукровий діабет, але потрібні подальші дослідження для з'ясування закономірностей. Перспективою подальших досліджень є визначення прогностичних факторів та ключових біологічних механізмів з метою прогнозування перебігу захворювання та розробки патогенетично обгрунтованих лікувальних протоколів.

Ключові слова: фіброзно-кістозна хвороба; прогностичні маркери; ожиріння; гормональний дисбаланс

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Introduction

An urgent global veterinary problem that remains unresolved is mammary gland neoplasms in dogs. Despite the positive results obtained, a dynamic increase in the incidence of the disease, a shift in the ratio of histological types towards malignant ones and an increase in mortality have been recorded in recent years. Egenvall et al. (2005) reported a mammary tumour incidence rate of 154 per 10,000, with an overall mortality rate of 6%. Vascellari et al (2016) reported an annual incidence of 250 cases per 10,000 dogs, with mammary neoplasia accounting for 54% of oncological pathology, of which 70% were malignant. The vast majority of malignant types among mammary neoplasia in dogs (77%) were confirmed by Dias et al. (2016).

Canine mammary tumours represent a naturally heterogeneous group of cancers that share several features with human breast cancer. These similarities include aetiology, activation of signalling pathways and histological classification. The use of natural canine breast tumours as a translational animal model for the study of human breast cancer is most promising (Gray et al., 2020).

Converting tumour characteristics into prognostic information is an invaluable tool for determining the most appropriate treatments and planning innovative therapeutic trials. In addition, spontaneous mammary tumours in bitches are a good model for studying human breast cancer. Collecting and interpreting information on the prognosis of canine and feline mammary tumours is challenging, as different methods have been used to study different components and characteristics (Matos et al., 2012).

Studies of the problem of fibrocystic disease in dogs are isolated, different in terms of content, have descriptive character, in most cases carry out on a small number of animals, or even characterize a clinical case. Currently, the main efforts of veterinary oncologists are directed at the study of tumours, while the initial stages of tumour transformation are ignored. Etiological factors, pathogenesis, and clinical-pathomorphological features of mastopathy in dogs remain understudied. The importance of the problem of mastopathy in bitches, which most oncologists classify as one of the forms of benign neoplasms, is due to the considerable spread and the particular importance of a potential source of cancer. There is a high possibility that proliferative changes in breast tissue as the form of correlation between epithelial and connective tissue elements, which can transform into cancer. Despite the scientific and practical importance of fibrocystic disease in dogs, the number of publications on this topic is small and has a descriptive character. In most reports, the problem of mastopathy is not considered separately but occupies a small part of studies of benign neoplasias in bitches (Ishenbaeva and Irgashev, 2019).

The validity of spontaneous canine cancer (CMC) as a natural model to study human mammary cancer (HBC) from a hormonal perspective has never been carefully investigated, making it impossible to use the results from humane medicine in veterinary. In particular, recent results show differences in estrogen and progesterone levels, which justifies the need for further research

The validity of spontaneous canine mammary cancer (CMC) as a natural model for the study of human breast cancer (HBC) from a hormonal point of view has never been thoroughly investigated, making it impossible to use data obtained in humans in veterinary medicine. In particular, recent results show differences in estrogen and progesterone levels, justifying the need for further research (de Andrés et al., 2022).

If the correlation of histological type and degree, age, clinical stage, and metastases in the lymph nodes with survival, the development of recurrences/metastases for mammary gland neoplasms in females is proved (Peña et al., 2013; Tran et al., 2016; Nunes et al., 2019), there are no similar studies regarding mastopathy.

Obesity has been identified as a risk factor for postmenopausal breast cancer in humans and is also suspected to be associated with a worse prognosis in bitches (Tesi et al., 2020). However, the study of the biological role of excess body weight in oncogenesis is at an early stage. A small number of studies have been published on the initiation of carcinogenesis in the background of obesity through inflammation (Marchi et al., 2022), metabolic dysfunction (ORMD) (Montoya-Alonso et al., 2017; Lyu et al., 2022) and increased expression of immune mediators (Shin et al., 2016).

The basis of dysplastic changes in breast tissue is a hormonal imbalance caused by endo- and exogenous factors related, in particular, to taking hormonal contraceptives, obesity and diabetes. The absence of pathognomonic clinical symptoms and defined prognostic markers causes difficulties in the early verification of mastopathy before its transformation into a malignant tumour. A more detailed study of the pathogenesis of mastopathy in bitches to develop and clinically implement effective diagnostic and treatment protocols, as well as preventive measures, remains relevant.

The study aims to determine the current state of the problem of mastitis in dogs and promising directions for its solution.

Fibrocystic disease in various species of animals

Along with the unstudied problem of mastopathies in dogs, some publications confirm its presence in other animals. Moreover, in productive animals, the coverage of the fibrocystic disease is limited to individual manuscripts.

Has been published a confirmed clinical case of fibroadenomatoid hyperplasia of the breast gland in a 12-month-old Holstein heifer. Clinical symptoms were demonstrated by dense multilobular foci in the right quarters of the udder, which was confirmed by the results of microscopy (hyperplasia of the mammary gland epithelium, numerous well-differentiated and moderately pleomorphic acini, moderate proliferation of myoepithelial cells and fibrous connective tissue) and immunohistochemical analysis (100 % showed immunoreactivity for p63, in 50 % – receptors for estrogen and progesterone, in 30 % – were positive for Ki-67 (Silva et al., 2017).

Have been reported about three rare cases of diffuse fibroadenomatoid hyperplasia of the breast gland in 10–12-month-old water buffaloes (Bubalus bubalis). Tumours were verified based on the results of clinical (consolidated foci on the background of diffuse oedema), morphological (pronounced hyperplasia of the breast gland epithelium, the presence of numerous well-differentiated moderately pleomorphic acini surrounded by proliferating fibrous connective tissue and myoepithelial cells) and immunohistochemical studies (positive immunostaining for cytokeratin, receptors estrogen and progesterone) (de Sant'Ana et al., 2014).

There are few manuscripts about the problem of neoplasms of the breast gland in horses and they are devoted only to the most common pathology – mastitis and carcinomas. Diseases of the mammary gland, the basis of which are fibrocystic changes in its functional tissue, remain out of the attention of scientists (Hughes, 2021).

A pathologically confirmed case of diffuse cystic mastopathy in a sterilized goat has been published. It has been reported that dysplastic lesions in goats and sheep have a multifactorial aetiology: the hormonal imbalance between estrogen and progesterone, genetic causes, and bacteria. At the same time, inflammatory diseases, such as mastitis and abscess, were excluded by clinical, thermographic, ultrasound and biochemical blood tests. As possible causes of the disease, the authors cite a hormonal imbalance between estrogen and progesterone, and genetically determined gene mutations (Schrank et al., 2017).

A histopathologically and immunohistochemically confirmed case of multiple neoplastic lesions of the mammary gland firstly was described in a Sudanese camel, although, according to the authors, single neoplasms are more characteristic of this animal species (Abeer et al., 2016).

A manuscript is presented describing a differentiated multinodular

infiltrative mass with multiple heterogeneous cystic areas filled with watery, opaque yellow contents in a 17-year-old female brown bear (Ursus arctos) (Vashist et al., 2013).

Neoplasms of the breast gland have been described in rabbits (laboratory and industrial breeds), their feature is a significant share of malignant types (88%), absence of cases of mastopathy among benign neoplasms, the same frequency of damage to cranial and caudal breast glands, peak incidence in 5–6-year-old animals, the peak of morbidity in 5–6-year-old animals (Baum and Hewicker-Trautwein, 2015). The opposite opinion is held by Schöniger et al. (2014), who draw attention to the high level of detection of tumour-like formations: among 17 females aged 2 to 8 years, lobular hyperplasia was diagnosed in two cases, and multiple cysts in ten.

It was previously thought that neoplasms in rabbits are sporadic, but recently, has been presented evidence of the regularity of occurrence of various types of tumours, primarily in breeds related to Oryctolagus. Currently, it is difficult to determine the real frequency of spontaneous neoplasms in domestic rabbits, based on the small risk of tumour formation at an early age. The Oryctolagus domestic rabbit has a lifespan of about 7–8 years, but in reality is much shorter due to use in research or commercial breeding (Tinkey et al., 2012).

Thus, mammary gland tumours do not have a proven species susceptibility, and the frequency of verification is probably influenced by the distribution and number of individuals of a certain species, as well as the lack of a single methodical approach to diagnosis.

Clinical and pathomorphological features of mastopathy in dogs

In the absolute majority of manuscripts, the authors provide statistical data on the prevalence of neoplasms and mastopathy in dogs by breed and age. However, such indicators reflect peculiarities of oncopathology within a certain territory and are largely subjective for the assessment of morbidity in other regions.

In dogs, neoplasms of the breast gland take second place in the structure of oncological pathology after neoplasms of the skin and its derivatives. Most of them are represented by half-breeds (23.5%), in the breed aspect - miniature schnauzers and standard dachshunds (11.9%). The proportion of malignant tumours was 85.3%, which in all cases were characterized pathomorphologically by areas of microcalcification. Ultrasound changes (heterogeneous hypoechogenicity against the background of the presence in some areas of cords with increased acoustic shadows) are not pathognomonic and do not allow exact determine the signs of a benign/malignant tumour or mastopathy (Salautin et al., 2019).

The population of domestic dogs is not used enough to study the problem of neoplastic changes in the functional tissue of the breast gland. Spontaneous neoplasm and dysplasia of the breast gland in dogs, despite similar histological and biological features with humans, differ in twice the frequency of registration and faster progression of the disease (Hahn et al., 1994).

Our previous research (2010–2012) established that, according to the veterinary medicine hospitals of Dnipro, fibrocystic disease accounted for 28.57% of all pathological changes in the functional tissue of the breast gland (Jesina and Bilyj, 2012).

According to a 12-year retrospective study of patients with oncology at the small animal clinic of the University of Veterinary Medicine and Pharmacy (UVMP) in Kosice, mammary gland lesions make up 5.8% of all cases. The peak morbidity was found in 10–14-year-old hybrids (24.7%), cocker spaniels (13.2%) and poodles (11.2%) (Valenčáková-Agyagosová et al., 2011).

The first retrospective statistical analysis based on a large number of clinical cases in China regarding the correlation between epidemiological clinical risks and histological diagnoses confirmed the high incidence of breast tumours in bitches (made up 46.71% of all cancer patients) on the background of approximately the same frequency of malignant and benign types (48.41% and 51.59%, respectively). In the absolute majority of cases, the patients are represented by 9–12-year-old non-castrated (77.38%) purebred (84.13%) bitches. The size of neoplasms in 47.82% is 0.5–28 cm, and malignant tumours were larger than benign ones (4.33 ± 2.88 vs. 3.06 ± 1.67, $p<0.001$). Multiple neoplastic lesions (44.64%) were verified as malignant in 74.67% of cases (Zheng and al., 2022).

The presence of clinical symptoms does not correlate with the verification of tumour changes by additional studies. In particular, based on the results of the clinical, cytological and pathomorphological examination of 127 females (Mysak et al. (2021) tumours of the breast gland were diagnosed in 80.3% of cases (102 animals). According to the results of histological examination, neoplasms of a malignant nature were found in 88 animals, or 69.3%, benign in 14 or 11.02 %, dysplasia was diagnosed in 25 or 19.7% of cases. The authors pay attention to a significant share: stage I neoplasia (according to TNM clinical classification) – 43.14% of patients, as well as animals with signs of fibrocystic disease – 19.7%. Retrospective analysis showed that in 40% of bitches, mastopathy is represented by a proliferative form with signs of microfocal tumour transformation.

The average age of dogs with breast gland dysplasia compared to malignant neoplasms is significantly lower, which is probably due to the earlier beginning of pathological changes in functional tissue. At the same time, with malignant tumours, the period from detection of the disease to the start of treatment is much shorter, which may be due to a more intensive progression and size of the pathological focus. The number of births in bitches with breast gland dysplasia was half less as with malignant tumours, against the background of the lack of difference in the frequency of false pregnancy and the period between the last birth and the detection of the disease factors (Mykhalenko and Kmitevych, 2019).

Two-year monitoring of dogs with cancer according to the method of Alston and Ellis (cytohistopathological studies) determines the proportion of malignant neoplasms – 86.7%, benign - 13.3%. Among the latter, mastopathy has been verified in 6.7% of cases (Shafiee et al., 2013).

According to the statistical analysis of the incidence of breast gland neoplasia in bitches, malignant histological types accounted for 64.28%, benign – 17.85%, non-neoplastic proliferative hyperplasia/ dysplasia – 17.85% against the background of correlation of p63 immunoreactivity with the degree of neoplasm aggressiveness (Patel et al., 2019).

Due to the results of research by other scientists, histological and pathological changes in the functional structure of the dogs' mammary gland in 72.16% were identified as malignant, 11.34% were benign, and 16.49% of cases – non-neoplastic proliferative/ dysplastic lesions. Immunoreactivity to smooth muscle actin (SMA) of tissues of malignant types is much higher, compared to benign and fibrocystic dysplasias (Raval et al., 2018).

Against the background of the discussion on many issues of the pathogenesis of mastopathy in dogs, reports on clinical cases of atypical morphological structure in fibrocystic disease are increasingly being published.

A complex breast gland adenoma with a rare histological structure, which is characterized by the differentiation of tumour cells in the sebaceous glands, was described in a 13-year-old unsterilized crossbreed female. On the background of squamous metaplasia were revealed isolated clusters of large «foamy» cells associated with basaloid reserve cells, similar to sebaceous glands. The expression of p63 in both sebaceous basaloid reserve cells and myoepithelial cells, and their structural continuity in the tumour tissue, indicates a common origin of these two components (Yasuno et al., 2013).

A clinical case of atypical breast gland adenoma in a 9-year-old Miniature Pinscher female is presented, the pathomorphological structure of which was characterized by the proliferation of a single-layered cystic duct consisting of basaloid cells with frequent

myoepithelial differentiation. Histological and immunohistological studies have shown that the origin of the tumour is related to progenitor cells of the mammary gland with a predominant differentiation into the myoepithelial progenitor line (Yasuno et al., 2011).

According to the histological and cytological assessment of dyshormonal dysplasia of the mammary gland (considered a precancerous condition), the pathogenetic role of the migration of neoplastic cells into blood and lymphatic vessels, which is of significant importance in the progression of the disease, is not taken into account (Kovalenko and Bilyi, 2021).

Therefore, a more in-depth study of the pathogenetic aspects of mastopathy in dogs remains a relevant direction for further research.

Hormonal imbalance is a key link in mastopathy

Fibrocystic disease (FCD), also known as «blue-domed cyst» or polycystic mastopathy, is considered one of the forms of breast dysplasia, characterized by duct extension and the formation of cavities. Most often, the fibrocystic disease pathogenesis includes a hormonal component, and the use of medroxyprogesterone, regression during metestrus confirmed by the high risk of its development. FCD is considered a benign formation in dogs, however, the disease was associated with the development of breast carcinoma (Solano-Gallego, 2010).

Clinical experience shows that the degree of risk of developing structural disorders of functional breast tissue in bitches is associated with the use of progesterone for the treatment of obstetric and gynaecological pathology (Zedda et al., 2017).

The importance of hormonal imbalance in the pathogenesis of fibrocystic disease was proven by the experimental administration of 2 % synestrol and 2.5 % progesterone in unsterilized female rats. Macro- and microscopic changes in the functional tissue of the breast gland, in particular, morphometric indicators corresponding to mastopathy, were checked (Diep et al., 2015). Experimental modelling of the development of breast gland tumours in Sprague-Dawley and Wistar rats with a single intraperitoneal injection of methylnitrosourea showed a high variability of the initiated neoplasia against the background of the presence of dysplastic precancerous formations of the breast gland in 22 % of the animals (Gal et al., 2011).

Publications indicate the presence of estrogen receptors (ER) and progesterone receptors (PR) in the absolute majority of cases of female mastopathy as well as a significant increase in the tumour marker CA 15-3 (Hasan et al., 2015). These data are consistent with the results of other research, according to which ER and PR were detected in 49 of 53 samples of benign neoplasms (PR). Six estrogen- and progesterone positive benign lesions verified normal mammary epithelium (may cause false-positive results for the presence of receptors), which correlated with ER levels ($r=0.28$, $p<0.05$) (Rutteman et al., 1988).

In bitches, ER expression is much higher in healthy tissues, hyperplastic/dysplastic lesions, and benign tumours compared to malignant neoplasms. The loss of expression of estrogen receptors is less pronounced in dog females than in cats. PR expression is not significantly different between normal tissue, dysplasia and benign tumours but is lower in breast cancer (Millanta et al., 2005).

Dysplastic changes in breast tissue can be caused by a hormonal imbalance conditioned by cholesterol metabolism disorders. Dyslipidemia was confirmed in patients with dysplastic and tumoral changes in functional tissue: an increase in the level of total cholesterol and triacylglycerols against a decrease in HDL cholesterol (Tymošenko and Kuz′mina, 2016).

A hypothetical multistep model of breast carcinogenesis suggests that invasive carcinoma arises from a series of intermediate hyperplastic lesions due to varying degrees of atypia and invasive carcinoma. Atypical hyperplasia (hyperplasia of the usual type, HUT) is an optional precursor of breast cancer (Shaaban et al., 2002).

Mechanisms of pleiotropic activation of ERα by estradiol, which is synthesized by the ovaries, play one of the primary roles in the pathogenesis of dysplasia. The essence of its effect is the modulation of intracellular signalling pathways with the initiation of post-translational modification of some proteins, which occurs due to genomic (gene transcription) and non-genomic effects (Torres et al., 2021).

Considering the conflicting reports of in vivo and in vitro studies on the main role of ovarian hormones in mammary oncogenesis in dogs Rao et al. (2009) confirmed that high levels of progesterone initiate hyperplasia of functional tissue. It was found that the expression of genes involved in cell proliferation increases in progestin-induced hyperplasia (PCNA, NPY, RAN; transcription factors and molecules of cell adhesion.

Was registered a direct relationship between the presence of in situ, invasive mammary gland carcinomas and the occurrence of atypical ductal hyperplasia. Ductal hyperplasia, more often without atypia, was found together with malignant neoplasia in 56 of 115 cases (48.8%). It has been shown the gradual loss of expression of proteins related to proliferation control (ER, EGFR) and E-cadherin in intraepithelial lesions, which indicates that canine mammary gland hyperplasia may play an important role in the process of malignant neoplastic transformation (Ferreira et al., 2012).

Unlike the protective, antiproliferative effect of progestins on the development of endometrial cancer, progestins can have a local stimulating and inhibiting effect on the proliferation of the mammary gland epithelium. There has not yet been a definitive molecular explanation for this discrepancy. Long-term treatment of dogs with depomedroxyprogesterone acetate (DPMA) or proligestone (PROL) results in increased plasma concentrations of growth hormone (GH), insulin-like growth factor (IGF)-I, IGF-II, and IGF-binding proteins along with the development of benign mammary tumours. Stimulated plasma GH levels do not have the typical pulsatile secretion and are not sensitive to GHRH stimulation or inhibition by somatostatin. Autonomic secretion can be inhibited by the antiprogestin RUU-486. The authors have shown that progestins in the mammary gland induce the expression of the gene that encodes growth hormone (Mol et al., 1996).

Against the background of the proven role of progesterone and estradiol in controlling the proliferation of mammary glands and the formation of neoplasia in dogs, remain little studied the enzymes that metabolize steroids and can act as regulators of their bioavailability. The last two control the proliferation processes of functional breast tissue. It was established that in cystic fibrosis, the expression of steroid metabolizing enzymes 5α-reductase and type II aromatase decreases, while in tumours, conversely increases significantly (Marinelli et al., 2004).

The influence of sex hormones on the biological links of neoplastic mechanisms in the mammary gland proves the fact that the frequency of the appearance of new tumours after ovariohysterectomy has decreased by approximately two times (from 64 to 36%) (Kristiansen et al., 2013) as well as an 80% share of non-sterilized bitches in the structure of morbidity (Zheng et al., 2022).

The role of obesity in the pathogenesis of cystic fibrosis

Currently, obesity is an actual problem, which is directly related to the increase in the number of cases of breast gland pathology in bitches. Obesity is an excessive accumulation of adipose tissue in the body and it's the most common disease of dogs in Ukraine and abroad. In recent years, there has been a negative trend of increasing the number of overweight and obese dogs. Most researchers agree that at least 33 % of dogs whose owners come to veterinary clinics are obese. Excessive accumulation of adipose tissue leads to metabolic and hormonal disorders, which are an important pathogenetic link in many diseases, including diabetes and breast tumours (Zoran, 2010).

In contrast to humane medicine, the long-term health risks of overweight and obesity in dogs are not well established and therefore need to be studied in detail (Weeth, 2016).

The risk factors for obesity in dogs, among which the most significant are sex (bitch), sterilization (ovariohysterectomy), age (average 5.7 years), breed (Yorkshire terrier, poodle, retriever, Rottweiler, German shepherd) also significantly increase the probability of tumour changes in the breast (Colliard et al., 2006).

In obese dogs, insulin resistance correlates with the degree of obesity, and weight loss improves insulin sensitivity. The concomitant decrease in TNF-α and adipose tissue mass suggests that in dogs, as in humans, this adipokine may be involved in insulin resistance in obesity. The proportion of adipose tissue in the body before weight loss is positively correlated with both concentrations: insulin in plasma (Kendall τ=0.30, p=0.044) and glucose/insulin ratio (Kendall τ=0.36, p=0.022), both indicators decreased after normalization of weight (p=0.0037 and 0.0063, respectively). Loss of body weight leads to a marked decrease in the concentration of tumour necrosis factor α (TNF-α), haptoglobin and C-reactive protein ($p<0.05$ for all), which indicates an improvement in the subclinical inflammatory state and, accordingly, a decrease in the probability of tumour transformation (German et al., 2009).

Based on the fact that in overweight or obese bitches, estrogen and progesterone receptor (HR) expression has been shown to correlate with aromatase, which, through interaction with adipocytes, enhances the progression of neoplastic transformation (Lim et al., 2015), it can be argued that such animals are at high risk of mastopathy.

In obesity, aromatase induction is possible in the following ways: activation of signalling pathways by an excess amount of adipose tissue in the body; by increasing production of TNF by adipose fibroblasts and the PGE by functional breast tissue. Further progression of changes in the breast gland occurs due to paracrine mechanisms (Bulun et al., 2012).

The existing theories of the carcinogenic mechanisms of obesity are based on the direct mutagenic effect of feed components and the violation of the balance of sex hormones. However, the results of recent studies indicate the possibility of initiation of neoplastic changes in the mammary gland due to chronic inflammation: through activation of the kynurenine pathway, which affects metabolism through activation of the aryl hydrocarbon receptor (AHR) and debilitation of tumour suppressor cells by serine proteases (Stone et al., 2018).

Published by Lim et al. (2022) study results indicate that obesity can affect the development and progression of breast neoplasms and is associated with a higher histological grade, greater infiltration by tumour-associated macrophages, and increased tumour angiogenesis. At the same time, quantitative indicators of stromal (sTAM) and total (tTAM) tumour-associated macrophages correlate with overall survival, which indicates that they can be used as prognostic indicators of mastopathy and mammary neoplasia in dogs (Monteiro et al., 2021).

Excess body weight in dogs can potentially cause the development of insulin-dependent diabetes mellitus, which is a risk factor for cystic-fibrinous disease. In particular, was proved the possibility of the development of diabetic mastopathy, which was characterized by changes in clinical, radiological and histological signs different from the generally accepted ones as a result of insulin-dependent diabetes mellitus (type 1) (Francisco et al., 2012).

The possible role of diabetes in the mechanisms of the development of pathological changes in the functional tissue of the breast gland in dogs is confirmed by other studies. Akhtardanesh et al. (2013) have proven that diabetes together with ductal ectasia and secondary infection with Pseudomonas aeruginosa complicate the course of mastitis with the formation of dense areas of connective tissue. The low and slow effectiveness of conservative treatment of such patients justifies mastectomy of the affected «packages» of the breast gland.

Summarizing the above information, it should be noted that there are no publications in veterinary medicine that would relate to the correlation of excess body weight with insulin-dependent diabetes and mastopathy.

Discussion

Mastopathies in dogs are currently a hot global topic. However, the main vector of research in veterinary oncology aims to study pathological changes in the mammary gland already at the tumour stage (Colodel et al., 2012; Baioni et al., 2017). At the same time, mammary dysplasia/hyperplasia, which should be considered a precancerous condition, has been overlooked by scientists.

Published data on age-specific susceptibility to tumour changes in dogs do not vary significantly, with the incidence of dysplasia/hyperplasia peaking at around 8 years, benign tumours at 10 years, and malignant neoplasms at 13 years (Zatloukal et al., 2005).

The frequency of mammary gland neoplasms in individual breeds varies considerably in the publications, which, in our opinion, is due to their territorial distribution. Therefore, the authors' claims (Komazawa et al., 2016) about breed predisposition are questionable.

Generally, benign and malignant mammary tumours have an equal frequency, but in recent years there has been a trend towards a significant increase in malignant types (Salas et al., 2015). Perhaps one reason is the lack of treatment at the initial stage of mastopathy.

As a rule, reports show a lack of correlation with the degree of invasion of clinical indicators such as age, reproductive status, and breed (Ariyarathna et al., 2022).

In the case of multiple lesions, neoplasms found simultaneously in dogs were more likely to have the same diagnosis and tumour types (benign or malignant), indicating a biological link between such neoplasms. Therefore, benign mammary hyperplasia should be predicted in the presence of benign neoplasia in bitches (Gunnes et al., 2017).

Although the study of mammary tumours in dogs is increasing every year, the exact risk factors are still unknown, but a combination of environmental factors, regional socio-economic factors affecting humans and their domestic companions, and animal housing factors probably play a role. In particular, castration has been negatively associated with the proportion of epithelial mammary tumours, and breeds native to the region have a lower risk of mammary tumours (Rodríguez et al., 2022).

An integral component of the study of the neoplastic process is its classification, which now requires updating in light of the latest findings on oncogenesis. The results of dysplastic and tumorigenic studies obtained in recent years indicate that the prognostic value of clinical and pathomorphological changes is declining. Convincing evidence for the need to adjust the TNM-WHO classification of clinical stages of neoplasia is the fact that 18% of malignant breast neoplasia types are less than 1 cm in diameter (Burrai et al., 2020). Although previous reports suggest that increased tumour size correlates with an increased grade of malignancy (Sorenmo et al., 2011; Bely et al., 2019). The proposed histological and cytological classification of hyperplasia/neoplasia, inflammation and cysts does not allow the determination of the malignant potential of a breast neoplasm. Pathomorphological changes show little correlation between biological behaviour and tumour prognosis (Matos et al., 2012). In breast dysplasia in particular, clinical and pathomorphological parameters do not correlate with immunohistochemical markers, constant expression of epidermal growth factor receptor (EGFR) in myoepithelial dysplastic and surrounding physiologically unchanged cells against a background of luminal cell negativity (Gama et al., 2009).

Progesterone is known to exert its action by binding to specific

receptors (PR) within the cell. But in dogs, unlike other animals and humans, there is no information on PR isoforms. Pilot studies using Western blotting and immunohistochemical analysis established the expression of both progesterone receptor isoforms (PR-A, PR-B) in bitches, with maximum staining intensity in areas of proliferation. A comparison of the amino acid sequence of canine and feline PR with human PR revealed significant differences in the PR-B-specific upstream segment (BUS) (Gracanin et al., 2012).

Translational and comparative oncology studies usually build on the similarities between human and animal cancer models. The general similarities reinforce these models and the differences complicate the research. However, it is not all so straightforward: the differences in the sex cycles of women and dogs, on the one hand, do not allow the «mechanical» transfer of information from human to veterinary medicine; on the other hand, they allow a different perspective on the interaction. The biological and molecular effects of oestrogen on target receptors and tissues are likely to be the same, enabling the study of cancer in an oestrogen-rich or oestrogen-deprived natural environment.

These results reflect the complexity of the role of oestrogen in cancer development and the plasticity of breast cancer cells and their ability to adapt to adverse conditions. Contrary to common belief, oestrogen can have a beneficial effect on a subset of breast cancer patients and cancer in general (Sorenmo et al., 2019).

Although it is clear that changes in cancer cells are similar in humans and dogs, the link between obesity and the risk or progression of cancer in veterinary medicine, unlike in human medicine, remains unproven. This is largely due to their retrospective nature and small coverage in the numbers of animals. They do not take into account the relationship between obesity (which is clinically characterised as a body condition score) and specific cancer diagnoses. Furthermore, the spectrum of cancer histopathology commonly observed in dogs does not include all cancers for which obesity risk associations have been identified in humans (Chandler et al., 2017).

The lack of molecular information on breast neoplasia hinders the identification of clinically relevant markers beyond histopathology and the introduction of new therapeutic concepts. Research aimed at studying the molecular basis of canine mammary tumours (DMCs) has long been constrained by the limited number of dog-specific molecular tools. In recent years, more molecular tools have been developed for dogs at the genome, RNA and protein levels, and an increasing number of studies are shedding light on specific aspects of canine carcinogenesis, particularly in the mammary gland. Furthermore, the potential use of the dog as a model for human breast cancer is controversial until questions regarding cellular origins, mechanisms and cellular pathways are answered (Klopfleisch et al., 2011).

Molecular aspects of tumours (metabolism, gene expression, miRNAs and transcriptome sequencing markers) are crucial for a proper understanding of tumour genesis and the application of individualised treatment options. Using a couple of the aforementioned markers together seems to be most useful for early diagnosis of tumour disease as well as for assessing treatment response, the presence of tumour progression or further prognosis (Kaszak et al., 2022).

Conclusions

One of the current problems in veterinary oncology is fibrocystic disease, which is diagnosed in many domestic and wild animals (dogs, cattle, horses, bears and camels). Mastopathy is most often seen in unsterilised bitches between 6 and 8 years of age, against a background of taking hormonal contraceptives. The disease is characterised by the absence of pathognomonic symptoms and the potential danger of dysplastic tissue transforming into a tumour. Among the risk factors for fibrocystic disease in bitches, the most clinically important are: impaired hormonal status, excessive body weight and diabetes mellitus.

A more detailed study of the role of obesity and its associated metabolic abnormalities in the pathogenesis of mastitis in dogs is a prospect for further research.

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