

CONTRIBUTIONS TO THE MORPHOLOGICAL STUDY OF MAMMARY TUMORS IN CARNIVOROUS ANIMALS

SUMMARY

The main objectives of the researches carried out in this thesis are: to identify the tumoral processes of mammary gland in pets and to classify them in accordance with their morphological characteristics; the revision of identification and labeling criteria of morphological types of mammary tumors; the assessment of identification criteria used as markers in diagnose and prognostic of general diseases and the possible correlation of these criteria with some environmental factors.

The doctoral thesis has 358 pages and is structured in two distinct parts: the first part, which included information published in scientific literature in relation with the topic of the thesis and the second part, referring to the results of personal research performed during the time of elaboration of the thesis.

The first part entitled *The level of knowledge regarding tumor disease*, is systematized in four chapters in which are summarized the information selected from 338 bibliographical sources referring to: the etiopathogenesis of tumor process, epidemiology of oncopathies, tumours classification and morphoclinical and histological characteristics of the principal types of mammary tumours in carnivorous.

The original part of the thesis, extended on 227 pages cover the materials and methods, the obtained results, the discussions of the results and the general conclusions.

The material of the study was represented by 75 dogs and 40 cats of female sex with abnormal formations in one or more mammary glands.

The investigations were made on a material sampled through intra- and postoperative biopsy from operated animals in university and private clinics (67,8 %), porbes sampled from animals necropsied in the pathologic anatomy laboratories (6 %), as well as on the pieces

shipped under the form of paraffin blocks and/or under the form of permanent eradicators (26 %), originated from the counties of Neamț, Botoșani, Suceava and Galați.

The samples collected intra- and post surgery by biopsy and at necropsy, were photographed and carded. From each case 3 to 17 samples were collected for histopathological examination. The samples (in some cases, the entire tumour) were fixed in formaldehyde 10% and/or Bouin liquid, refined, refixed, embedded in paraffin and sectioned at 5-6 μm .

Furthermore, samples sent for diagnosis from Neamț, Botoșani, Suceava, Galați counties were processed and examined.

From about 750 samples 7500 histological sections were prepared and 6000 stained through various usual and special methods like: HEA, PAS, HE, Pappenheim, PAS-alcian blue, Alcian blue, Toluidine blue, Gömöri silver impregnation, Giemsa sulfation, Orcein and May-Grünwald-Giemsa.

The histological sections stained by various methods, enlightened and mounted in Canada balsam were examined at optical microscope and were photographed at various optical resolutions.

The histopathological examination of permanent sections resulted from samples processing has allowed, according to the hierarchical and morphological of the lesions classification criteria described in veterinary pathology, the identification and classification of the lesions of mammary gland in dog and cat. Thus are presented and successively illustrated the subsequent groups of lesions: non-proliferation lesions associated to the tumors, benign proliferative lesions forerunners to the tumors, benign mammary tumors and malignant mammary tumors.

The non-proliferative lesions associated to the identified tumors were: cystic change, duct ectasia, metaplastic change of epithelium and stroma, fibrosclerosis, collagenous spherulosis and calcification.

Proliferative lesions forerunners to the tumors, identified at both species, were: intraductal and lobular epithelial hyperplasia (alveolar or acinar), adenosis and fibrocystic disease. It are described microglandular adenosis, more rarely, with prevalent multiplication of glandular structure and sclerosing adenosis, the most frequently, characterized in the massive fibrosclerosis and hardening of central tubules and dilatation peripheral tubules.

Fibrocystic or sclerocystic disease, diagnosed in six dogs and two cats, manifested in mono- or multicentric pseudotumors with variable sizes, is characterized *histopathologic in*

début at TDLU, cysts formation from glandular components, pericystic fibrosclerosis, microglandular adenosis and microcalcification, complicated sometimes with metaplasias of the stroma and inflammatory reactions as is the foreign body granuloma. Fibrocystic disease is correspondent of the human Reclus disease. Histopathological description of lesion is omitted in Romanian oncoveterinary pathology and sporadic and incompletely described in foreign pathology.

In the category of **benign mammary tumors** were described tumors with origin in epithelial component: papillomas, adenomas; with origin in mezenchymal component (fibroma, leiomyoma) or in both (fibroadenomas and proper mixed tumors).

True or centered papillomas, localized in ductal system, can be simple or pure, complexe and sclerosing. The torsion and necrosis of central papillomas generate microhaemorrhages and hematotelia, the clinic symptom of bleeding nipple being useful for diagnosis in the case of canine papilloma, too.

The adenomas were identified at four dogs and two cats. It were described ductal and lobular, glandular and mioepithelial, simple (pure) and complex adenomas .

Rarely in human oncology, unknown among carnivorous masthopaty, we have identified sudoriferous mammary adenoma (hidrosadenoid or apocrine) constituted from both histological variety: glandular and ductulo-papillary.

The mezenchymal tumors were identified in two dogs as fibroma and leiomyoma.

The fibroadenomas, as benign epitheliomezenchymal tumors, were identified at both species, either as principal tumors in five dogs and three cats, either as association lesions in ten cases.

The pericanalicular, periductal, hard fibroadenoma is characterized through histological surrounded by a capsule, epithelial hyperplasia like a secretory tubes and mezenchymal, peritubular with concentric arrangement, mixomatous change of the stroma, appearance more clear at cat.

The intracanalicular, vegetative, or softly fibroadenoma, epithelial hyperplasia is continued by mezenchymal hyperplasia like connective -capillary buds with centripetal growth what determined the deformation, hardening or stopping of lumen, in association with ramification and distortion of the tubes, microcalcifications and mixomatous change of the stroma. The evolution of fibroadenoma is either at delivery or in intracanalicular type, at malignization in *phylloides* tumor, characterized by sarcomatous appearances, epithelial hyperplasia with atipya and mitoses, infiltrative growth, local relapse and, occasionally metastasis.

The benign mixed tumors, histopathological identified in dogs are neoformations in which structure were founded epithelial, mioepithelial and complex adenomas associated with mezenchymal cells and various conjunctive tissues: fibrous, cartilaginous, bony and/or adipose, and sometime hematopoietic.

The category of malignant mammary tumors includes epithelial tumors or carcinomas, mezenchymal tumors or sarcomas and mixed tumors, epitheliomezenchymal or carcinosarcomas.

The malignant epithelial tumors were presented according the systems of classifications recommended by oncological reference material.: carcinomas and adenocarcinomas (with grouping of cells around the lumen) non-infiltrative (noninvasive, pre-invasive, intra-membrane or in situ) and infiltrative (invasive); pure (simple in majority) and impure (mixtures of displasias and of benign epithelial proliferations, of various types and subtypes); lobular and/or ductal ; classical (commons) and of special type.

The simple carcinomas (tubulo-papillary, solid and anaplastic), formated by only one type of epithelial cells, are the most frequent mammary neoplasia in dogs and cats. The complex carcinomas was signaled just at dog.

The *in situ* lobular carcinoma, diagnosed in three dogs and one cat, has three defining features: keeping of the lobular architecture, distended and obstruction of alveoli by proliferations of epithelial cells, monomorphe, monotone and noncoesive, vacuolated frequently, with rarely mitosis and minimum reaction of stroma.

The *in situ* ductal carcinoma of solid type were identified in seven dogs and one cat and is characterized in obliteration of some extralobular duct with proliferated epithelial cells, with growth mitotic activity.

Furthermore it were diagnosed: *in situ* ductal comedocarcinoma, frequent in both species, *in situ* cribriforme type ductal carcinoma, more frequent in cat, micropapillary and proper papillary in situ ductal carcinoma, noninvasive papillary cystadenocarcinoma, identified in both species.

The extramembrane, invasive, infiltrative carcinomas constitute a group of malignant epithelial tumors with one large scale of morphologic phenotypes, characterized in marked tendency for metastasis in extra-mammary zone.

The invasive carcinomas and adenocarcinomas, frequently at both species, were identified and described in dogs and cats, with ductal and lobular localizations.

The typical invasive component of lobular carcinoma is formed by migratory neoplastic cells, solitary or organized in divergent or concentric monomas, included in fibrous

or/and scyrous stroma.

Indifferently of type of original ductal carcinoma, invasive component is represented by thin cords, thick anastomosed trabeculae, nests and plaque low delimited or solid mass.

The ductal anaplastic carcinoma, identified at one dog and two cats, is characterized by hyperplasia of anaplastic malignant cells, inconstant cohesive, multinucleated and nucleolated, with a higher mitotic index and myoepithelial cells are absent in ducts, apparently surrounded by connective tissue, lymphoplasmacytic infiltrate and invasive component in the shape of girdles and tubes.

In the category of carcinomas and adenocarcinomas of special type were included: spindle cell carcinoma, rare tumor, identified at two mature dogs; complex carcinoma, relatively frequent at dog, absent at cat; the epidermoid carcinoma (with squamous differentiation), identified at dogs; the mucinous carcinoma, diagnosed in a bitch and a cat; colloid carcinoma, tubular carcinoma, carcinoma with clear cells etc.

The colloid carcinoma, synonymous with mucinous carcinoma, presented in human oncological reference material, unknown as such in available veterinary oncology literature was identified in a 13 month age cat.

In the bitches, in the category of tumors with clear cells, on the basis of histological particularities mentioned in oncopathology, were identified the sebaceoma or the sebaceous epityoma, the solid carcinoma with clear cells, and the sudoriferous cystadenocarcinoma.

In the category of malignant mesenchymal tumors were diagnosed:

- the fibrosarcoma at three dogs, characterized by proliferation of spindle cells with elongated nucleus, interspersed by reticulin and collagenous fibers;
- the osteosarcoma at a eleven years old German Shepherd female and characterized by the proliferation of sarcomatous cells with osteoid and bone marrow formation;
- the angiosarcoma, malignant tumor of blood and lymphatic vessels, at a nine years old German Shepherd female, and
- the mammary liposarcoma at a ten years old Spanish Cocker.

The relapse of a mammary tumor surgery extirpated had the appearance of a adenocarcinoma by high malignity with pleomorphic cells, mitoses and scyrous stroma.

Analysing the morphological observations, can be formulated a few epidemiological considerations. Carnivores taken into consideration in the study were company animals, mostly, or with rogue habitat and with unsure origin. All of the tumor carrier animals were of females (100 %).

The frequency of the mammary tumors was with 50 % bigger at dogs then at cats.

Uniglandular localizations (68,3 %) affected, in the decreasing order of the frequency, breast M3, M4, M5, M1 and M2 at dogs, M2, M4, M1 and M3 at cats. In the polycentric forms the biglandular localization prevail and only at one bitch the tumors developed in all of the glands from both of the mammary rows.

Reported to the age, the frequency of the mammary oncopaties was bigger in cats under 2 years old and at the aged animals of both species and with maximal values between 6 and 12 years at dogs and between 4 and 8 years at cats.

Regarding the strain predisposition, at dogs the bigger frequency was recorded at the common strain (42,8 %) followed by the Cocker, German Shepard, Canish, Pekinez, Boxer a.s.o.; and at the common cat strain (65,5 %) followed by the Birmanese and Siamese strain.

The pure proliferative lesions were identified at 50 % from the total of mammary oncopaties at dogs and 40% at cats with mammary tumors.

The pure benign tumors were identified at 46% of the total of the mammary oncopaties at dogs and at 17% of the mammary tumors at cats, and the malign tumors, at 54 % of the dogs and 83% of the cats. The epithelial neoplasia are 2,8 times more frequent (73,6 %) then the mesenchimals at dogs and 14 times more frequent (93,3 %) at cats.

The mammary tumor processes at dogs are characterized by a remarkable lesional polymorphism; at 50 % form the old females with bulky tumor masses, benign and malign lesions, untumoral proliferative lesions and associated unproliferative lesions, accompanied by calcifications, hemorrhages, necrosis, inflammatory reactions, secondary infections were identified in variable proportions a.s.o.

The thesis ends with 40 conclusions in which there are exposed tersely the main lesions of the mammary glands identified by anatomopathological and histopathological investigations, and their degree of originality and importance in the direct and differential diagnosis in dog and cat.

The thesis is very well illustrated by 227 original color photos.