Canine Mammary Carcinoma

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Introduction

Mammary tumors are the second most common group of neoplasms in dogs, following skin tumors (Fig. 1).[6] They are the most common tumors in female dogs, comprising 52% of all neoplasms.[3] Of the mammary gland tumors diagnosed in female dogs, 41 to 53% are diagnosed as malignant.[7]

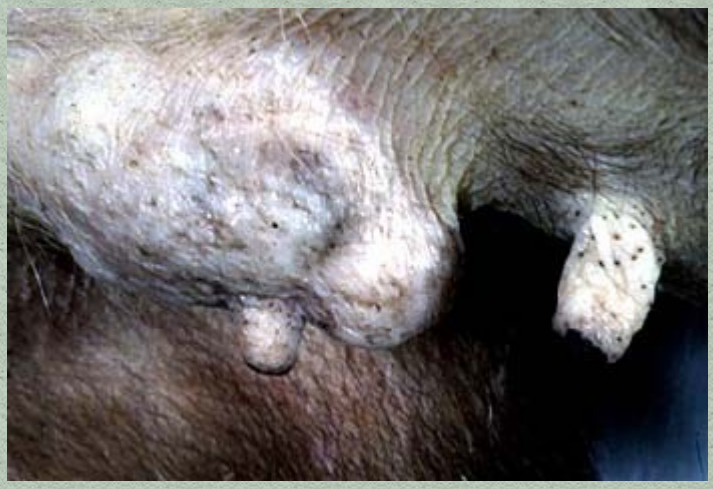

Figure 1. Clinically, mammary tumors often appear as tissue nodules or enlargements within the mammary glands (image courtesy of Noah's Arkive, University of Georgia).

Predisposition

The median age for diagnosis of mammary tumors in dogs is 10 years; neoplasms rarely occur in dogs < 4 years of age.[7] At 6 years of age, the risk of developing a mammary tumor appears to increase markedly.[6] It also appears that after 14 years of age, the incidence of benign mammary tumors levels off while the incidence of malignant cancer continues to

increase.[3]

The development of mammary gland neoplasms appears to be hormone-dependent because the risk of developing a mammary tumor increases as the number of estrous (heat) cycles increases. The risk of developing mammary gland tumors is 0.05% if the dog is spayed prior to the first estrous cycle. The incidence of neoplasia increases to 8% if the dog is spayed prior the second estrous cycle and to 26% if spayed after the second estrous cycle. An increased incidence of tumor development also has been observed in dogs that received injectable progestins for the prevention of estrus.[7]

Normal mammary tissue and a majority of benign tumors express both estrogen and progesterone receptors. Less than 50% of mammary carcinomas express either of these receptors. This observation suggests that there is a loss of hormone dependency during transition to malignancy.

Breed predisposition in the development of mammary neoplasms has been reported but varies in different studies.[5] Several of the spaniel breeds, poodles, and dachshunds have been reported to have an increased incidence of mammary neoplasia. Mammary gland tumors also have been observed in male dogs, but the incidence is 1% or less.[7] Affected male dogs usually have a hormonal imbalance such as an estrogen-secreting Sertoli cell tumor of the testis.[6]

Clinical Signs

Mammary tumors can occur as single or multiple nodules within a mammary gland or chain. These nodules are present in > 50% of dogs with mammary neoplasms. The majority of mammary gland tumors occur in glands 4 and 5 (60-70%), possibly due to the fact that the two most caudal pairs of glands contain the most mammary tissue.[6,7]

Mammary tumors can metastasize to regional lymph nodes, such as the inguinal lymph nodes (Fig. 2). This can lead to afferent lymphatic blockage causing edema of the limbs (usually the rear limbs). Metastases can continue to the pudendal and the internal iliac lymph nodes causing pressure and stenosis of the colon.[7] In some instances, retrograde growth of mammary gland carcinomas has extended as far as the stifle joint, obstructing lymph flow.[3]

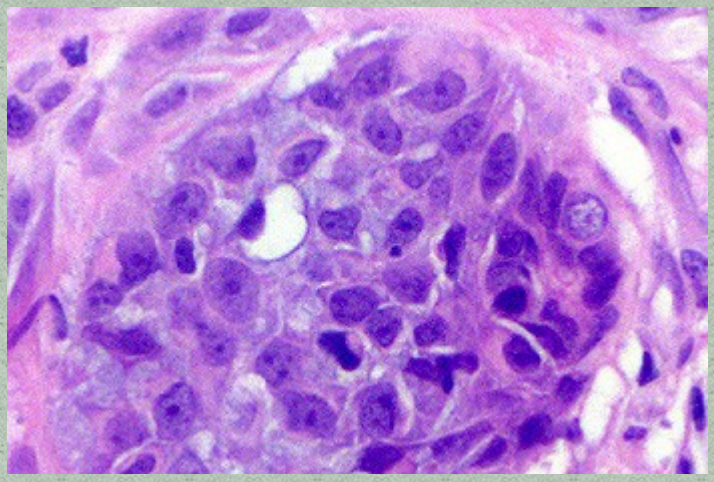

Figure 2. Histologic section of an inguinal lymph node that has been obliterated by metastasis of a mammary carcinoma (hematoxylin and eosin stain).

Mammary carcinomas may exhibit rapid growth, doubling in size within a few weeks. However, the size and appearance of these neoplasms can vary greatly.[6] Inflammatory carcinomas usually have diffuse involvement of multiple mammary glands. Edema, erythema, and firmness may be present and affected mammary glands may feel warm to the touch. Dogs with inflammatory carcinoma are more likely to have generalized weakness with anorexia and weight loss.[1] Inflammatory carcinoma is often misdiagnosed as acute mastitis.[7]

Normal Mammary Gland

Canine mammary glands are located in the subcutaneous fat layer of the ventral body wall. Mammary glands actually constitute five pairs of modified sweat glands that run in bilaterally symmetrical rows from the cranial thorax to inguinal region. They are composed of secretory acini and a series of excretory ducts. During lactation, the glands undergo hypertrophy, produce colostrum, and eventually produce milk. Normal secretions from mammary glands consist of a large amount of protein and lipid droplets. This secretory product is usually of low cellularity, containing a few foam cells admixed with fewer lymphocytes and neutrophils. Foam cells are large, vacuolated epithelial cells with a round to oval, eccentrically placed nucleus. These cells resemble actived macrophages. A normal aspirate of mammary tissue frequently is acellular or consists only of blood. If mammary tissue is present, the secretory cells have a uniform size, a dark nucleus, and a moderate amount of basophilic cytoplasm (Fig. 3). These cells may be arranged in an acinar pattern. Ductal epithelial cells are arranged in sheets, myoepithelial cells are spindle shaped, and adipocytes are balloon-like in appearance. Lipid droplets also may be present in a normal fine-needle aspirate of mammary tissue.[5]

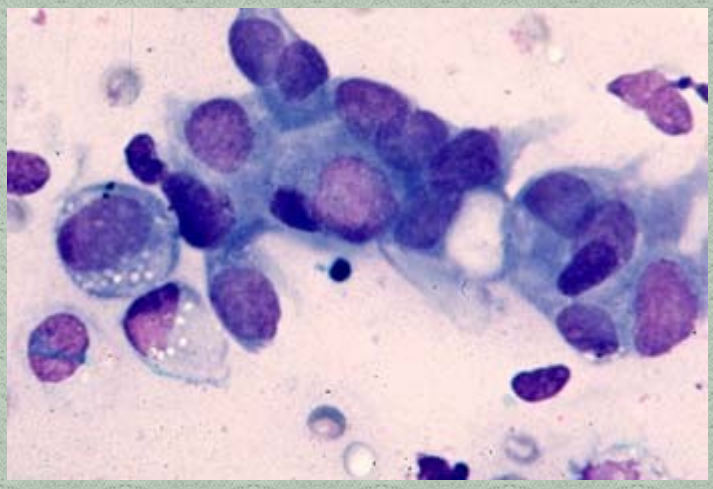

Figure 3. Aspirate from a normal mammary gland containing columnar epithelial cells and a few sparsely vacuolated macrophages (Wright stain).

Diagnosis of Mammary Gland Tumors

Mammary gland tumors are difficult to diagnose by routine cytology. Furthermore, it can be very difficult to determine the malignant potential of mammary neoplasms cytologically, and histological evidence of malignancy does not always imply an aggressive clinical course of disease.[5] Mammary hyperplasia, dysplasia, adenomas (benign neoplasms), and well differentiated carcinomas (malignant neoplasms) can have a variable morphologic appearances (Fig. 4). Cytologic differentiation of these lesions may be difficult to impossible, leading to false positive and negative diagnoses of malignancy.[9]

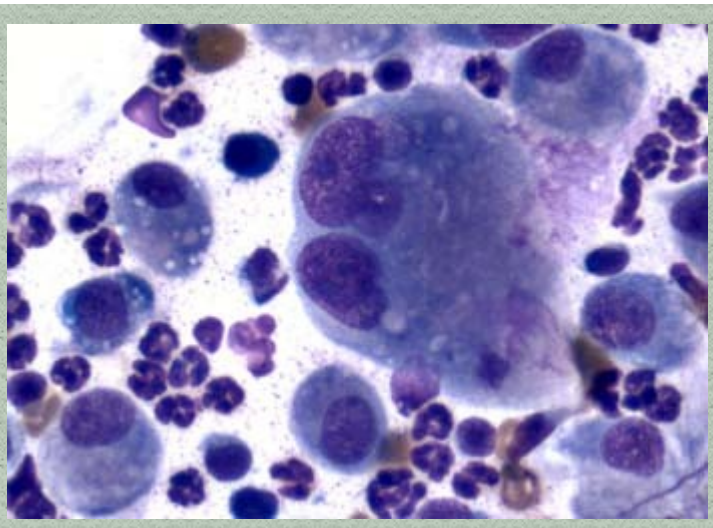

Figure 4. Fine-needle aspirate from a dog with mammary dysplasia and mastitis. Notice the variability in the mammary epithelial cells and numerous neutrophils. These lesions are best diagnosed by histopathology (Wright stain).

In one study, approximately 50% of all the mammary tumors examined had an inconclusive cytological diagnosis. Also, approximately 50% of the benign tumors and 25% of the malignant tumors were given a concordant cytological diagnosis. More specifically, 8 of 17 mammary carcinomas were given a concordant cytological diagnosis, and two adenomas were misdiagnosed cytologically as carcinomas (Fig. 5).[2]

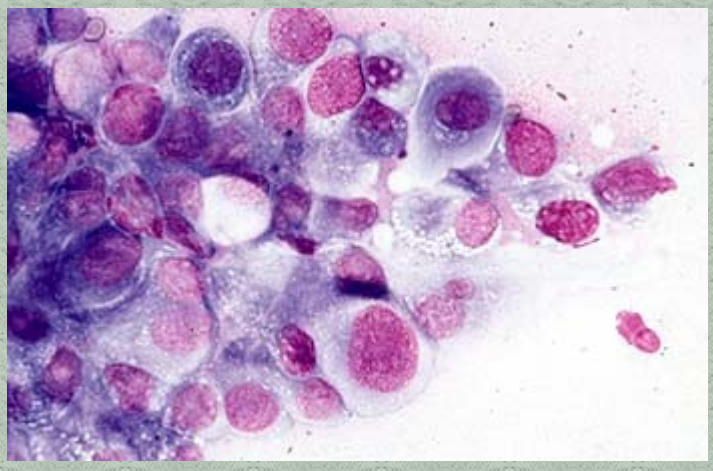

Figure 5. Fine-needle aspirate from a mammary carcinoma in a dog. Mild variation in cell (anisocytosis) and nuclear (anisokaryosis) size are present (Wright stain).

In another study, 147 skin neoplasms were evaluated cytologically using fine-needle aspiration. Of these neoplasms, 105 (74%) had the same cytological and histological diagnoses. However, mammary carcinomas were identified correctly in only 8 of 19 aspirates (42%). Two massed that were diagnosed cytologically as malignant neoplasms actually were benign.[4]

Cytologic material may be collected from a mammary gland for microscopic evaluation by expressing material directly from the gland or by fine-needle aspiration using a 22 gauge needle. If a fine-needle aspiration is performed, several aspirates should be obtained from

the same tumor. Furthermore, aspirates should be obtained from all tumors because more than one type of tumor may be found and considerable tissue heterogeneity may occur within a given tumor. Cytologic aspirates should be taken from the periphery of the tumor because necrotic tissue may be found in the center of the mass. Aspirated material should be smeared on a slide and allowed to air dry before staining. A tissue imprint or direct tissue smear also may be obtained, but these types of preparations often reflect surface inflammation, lack cellularity, and give no indication of tissue architecture.[7]

Cytologic Criteria of Malignancy

In a study performed to cytologically differentiate benign from malignant tumors, ten criteria for malignancy were determined. Anisokaryosis (variation in nuclear size), or lack thereof in benign tumors, was found to be a significant criterion of malignancy. In benign conditions, 83 to 86% of the specimens lacked anisokaryosis. Tumor giant cells rarely were found in benign tumors. Although not commonly seen, nuclear or cytoplasmic membrane distortions were significant when observed. In addition, a high nuclear to cytoplasmic (N:C) ratio was a significant criterion for malignancy for one of the cytologists in the study, but a poor indicator for the other cytologist. Irregular chromatin shape and size were used to help differentiate benign from malignant lesions. Nucleolar appearance was a helpful criterion in predicting malignancy, especially if macronucleoli were observed (Fig. 6). Variations in the number and shape of nucleoli also were a useful criteria of malignancy. Finally, parachromatin clearing was moderately significant cytologic criterion of malignancy (Table 1).

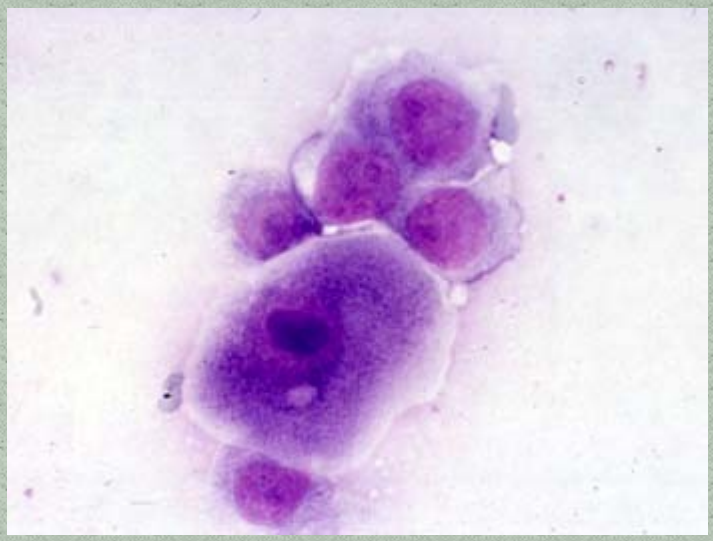

Figure 6. Macronucleolus in a neoplastic mammary epithelial cell (Wright stain, image courtesy of Noah's Arkive, University of Georgia).

Table 1. Cytologic criteria of malignancy in mammary neoplasms.

Anisocytosis (variable nuclear size)
Nuclear giant forms
Nuclear or cytoplasmic membrane distortions
High nuclear to cytoplasmic (N:C) ratio
Irregular chromatin shape

Variable chromatin size

Presence of macronucleoli

Variation in nucleolar number

Variation in nucleolar shape

Parachromtin clearing

Poor indicators of malignancy included poor intercellular cohesion, abnormal nuclear shapes, nuclear molding, abnormal multinucleated cells, and degree of cellularity. Abnormal mitotic figures rarely were seen but were thought to be of significance when noted. Using these criteria to evaluate the mammary malignancy does not predict cancer-associated mortality.[2]

Note: All cytologic diagnoses of mammary neoplasia should be considered tentative until confirmed by surgical biopsy and histopathology.

Cytology of Malignant Mammary Gland Tumors

Adenocarcinoma - Cytologically, cells from adenocarcinomas may exfoliate in sheets or clusters. Individual epithelial cells contain a round to oval, eccentrically-placed nucleus and a moderate amount of basophilic cytoplasm. The cytoplasm may contain amorphous basophilic secretory product and/or vacuoles. Acinar arrangements of epithelial cells also may be observed.

Anaplastic carcinoma - These neoplasms yield very large, extremely pleomorphic epithelial cells that occur as single cells or as small clusters of cells. Unusual nuclear and nucleolar shapes may be seen. Multinucleated tumor cells and abnormal mitotic figures also may be observed.

Inflammatory carcinoma - Cytologically, specimens from inflammatory carcinoma have focal clusters of cells, occasionally accompanied by stromal collagen. These neoplasms are locally invasive with a very aggressive clinical course. Microscopically, cytologic specimens from these neoplasms contain large, pleomorphic, epithelial cells; many nondegenerate neutrophils; and macrophages.

Squamous cell carcinoma - Squamous cell carcinoma of the mammary gland has a similar appearance to similar neoplasms that arise in the skin and other sites of the body. The nuclei of individual neoplastic cells range from small and pyknotic to large and round. Nucleoli are prominent and may be large and round to angular. The nuclear to cytoplasmic (N:C) ratio is variable. Binucleated and multinucleated tumor cells may be observed occasionally. The cytoplasm appears moderate to deep blue and has a smooth texture with occasional vacuoles. These changes are associated with keritinization.

Malignant Mixed Mammary Tumor - Epithelial cells and individual spindleoid cells of mesenchymal origin can be observed in cytologic preparations. One of these cell populations usually will display nuclear and/or cellular criteria of malignancy. Occasionally, pink chondroid or osteoid matric may be observed.

Carcinosarcoma - Epithelial and mesenchymal populations of cells with criteria of malignancy are found in cytologic preparations.

Sarcoma - Sarcomas are malignant neoplasms of mesenchymal cell origin. These neoplasms exfoliate poorly, yielding samples of low cellularity. In general, the cells are spindle to irregularly shaped, and are scattered individually or in small clumps. The cytoplasm is

moderately to intensely basophilic with attenuated to indistinct cellular borders. Mammary sarcomas are rarely diagnosed cytologically in the dog.[7]

Treatment and Prognosis

Note: Treatment of animals should only be performed by a licensed veterinarian. Veterinarians should consult the current literature and current pharmacological formularies before initiating any treatment protocol.

The initial workup of all dogs with mammary neoplasms should include a complete history including age, neuter status including age of neuter, date of last estrus or pregnancy, and any hormone treatment received. A thorough physical examination should be done.

Laboratory testing should include a complete blood cell count and serum biochemical profile. A coagulation profile should be performed in dogs suspected of having inflammatory carcinoma or that have a high risk of metastasis because of the associated risk of disseminated intravascular coagulation (DIC).

Thoracic radiographs, including both lateral views, should be performed to check for signs of metastasis (Fig. 7). Metastasis can occur to local lymph nodes, so these nodes should be palpated and/or aspirated, if possible.[7] Mammary glands 1, 2 and 3 drain to the axillary lymph nodes, while glands 4 and 5 drain to the inguinal lymph nodes. Owners of dogs that were spayed at > 3 years of age can assist in detecting mammary gland neoplasms by palpating the dog's mammary gland chains once a month. However, most neoplasms must be at least 1cm in diameter to be palpable.[3]

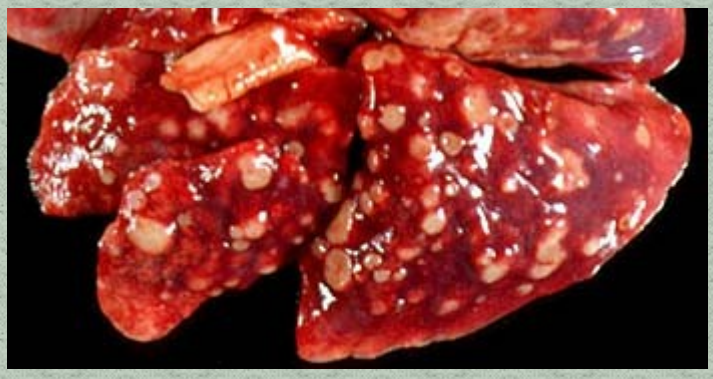

Figure 7. White, metastatic nodules of mammary carcinoma in the lungs of a dog that died of cancer (image courtesy of Noah's Arkive, University of Georgia).

The first choice of treatment for mammary gland neoplasia is surgical excision. The goal of surgery is to remove the entire neoplasm by the simplest procedure available. There is no difference in recurrence rate or survival time when a simple versus a radical mastectomy is performed. Also, it does not appear to be of benefit to spay the dog at the time of the mastectomy surgery. An effective chemotherapeutic protocol has not been reported. There is no reliable information on the value of radiation treatment, although it may be useful in dogs that have tumors that are too extensive for surgery.[7]

In one study of 33 dogs with mammary neoplasia, 5 dogs either died or were euthanized because of their disease, presumably within the first year of observation. One year after surgery, 19 dogs were still alive, 5 had been euthanized or died of causes unrelated to mammary cancer, and 4 dogs were lost to follow-up.[2] This indicated that the overall death

rate in a group of dogs with diagnosed mammary neoplasia was 15.2%.

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Image of Raven at the top of the paper is courtesy of owner Allison McCarthy.

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