

MAMMARY GLAND TUMORS

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General Information

Mammary gland tumors (MGT) are some of the most common tumors seen in veterinary clinical practice. They are the most common tumor seen in the female dog and the second most common tumor of the female cat. The risk of development of a MGT is well known to be increased in dogs that have not undergone ovariohysterectomy at an early age (Schneider et al, JNCI 1969). When compared to an intact female, the risk of development of a MGT in dogs spayed before their first heat, after their first heat and after their second heat is 0.05%, 8% and 26%, respectively. Importantly, this study did not find any reduction in MGT incidence in dogs spayed after their third heat. Early spaying of cats results in only a 50% reduction in MGT incidence, however a recent study suggests the protection is more like four-fold. The culmination of these studies strongly suggests that hormones influence the development of MGT in dogs and cats. In keeping with this tenet, the use of hormones such as synthetic progestins and progesterone has also been found to increase the risk of benign MGT formation in dogs. Though little work has been done to delineate additional risk factors, obesity and home cooked meals has been found to increase the risk of development of MGT in dogs. There are likely genetic influences concerning the etiopathogenesis of MGT in dogs and cats, however, very little research has been done in this area to date.

Pathology

The pathology of MGT in dogs and cats can be remarkably different. In dogs, approximately 50% are benign and 50% malignant, whereas in cats, 90% or more are malignant. Most MGT in the dog and cat are epithelial in origin (ie adenoma or carcinoma), however, carcinosarcomas and sarcomas are occasionally noted. Mixed mammary tumors are benign tumors of epithelial and mesenchymal origin that extremely common in the dog. A number of histologic classification schemes have been reported, however, the various histologic categories do not generally make a difference in prognosis clinically. That said, ductular carcinomas and carcino-sarcomas are well known to behave in a more malignant and metastatic fashion. In addition, grade and degree of differentiation have been found to be of prognostic importance in multiple studies. A rarely seen canine MGT subcategory termed Inflammatory Mammary carcinoma (IMC) is diagnosed by histologic and clinical criteria including the presence of a MGT, erythema and/or bruising of the overlying skin, as well as potential blockage of lymphatics in the local area with possible pitting edema of one or both hindlimbs. IMC is an extremely malignant MGT of the dog that routinely has a grave prognosis as most dogs have overt metastasis, or develop overt metastasis, within a very short period of time from presentation.

History & Clinical Signs

Dogs have 5 mammary glands, whereas cats have only 4 mammary glands. Interestingly, approximately 60-70% of MGT in dogs and cats occurs in the caudal most 2 mammary glands. In addition, approximately 50% of dogs as well as cats will have a solitary MGT, and the other

half will present with multiple MGT. Dogs with multiple MGT on presentation will generally have tumors in a variety of locations, whereas cats with multiple MGT will have multiple tumors within a mammary chain. Though exceptions will always occur, most benign MGT in dogs are small, firm, and well circumscribed lesions that are not adherent to underlying tissues. In cats, because benign tumors are extremely rare, it is important to differentiate the typical malignant MGT from benign mammary fibroadenomatosis (BMF). Cats with BMF are generally younger cats that are intact females, and pregnancy is commonly noted. Administration of progestins can also be a common historical feature of cats with BMF. While multiple mammary glands in feline BMF are generally swollen and many times painful on palpation, single glands can occasionally be affected in older cats. BMF will generally resolve with cessation of progestin administration and/or spaying. Occasionally, surgical removal of cats with single mammae BMF must be performed if spaying does not resolve the condition.

Diagnosis & Staging

The size of a MGT on presentation can be extremely variable. It is very important that the clinician remember to measure the diameter of the tumor(s) and place this information in the medical record. In addition, a simple description of the MGT is in order, as ulceration and other factors can be prognostic. Approximately 50% of feline MGT are ulcerated at the time of presentation. It is also important to palpate all local lymph nodes, especially the inguinal, axillary and prescapular lymph nodes in dogs and cats suspected of having MGT. If lymphadenopathy is present, a fine needle aspirate (FNA) and cytological examination should be performed; however, palpation is a relatively insensitive measure of lymph node metastasis and considerations should be made for LN FNA/cytology independent of whether the lymph node is palpable or not. In addition, any other abnormalities on physical examination (PE), especially lameness or other masses should be fully worked up to ensure they are not metastases of the MGT. In addition to that listed above, a thorough PE, a CBC/platelet count, small animal diagnostic profile and UA (retroviral and thyroid testing as well in cats) should be performed. Similarly, 3-view chest radiographs should be also be performed. An abdominal ultrasound should also be strongly considered, especially for dogs with caudal MGT or any cat with MGT, since ~ 25% of cats can have abdominal metastases of their MGT. In addition, to further delineate the problem at the suspected MGT site, an FNA/cytology of the mass should be performed to determine if the mass is a MGT, some other type of tumor or a non-neoplastic process. This is extremely controversial; however, this author feels strongly that one should start with an FNA/cytology. Though the cytological examination may have difficulty discerning benign from malignant, the result will tell the clinician with high probability if some other process is ongoing and then an appropriate workup/staging can then be performed. For example, a mast cell tumor that just happens to be in the general mammary area will be staged and treated potentially very differently than a mammary gland tumor.

Treatment

Surgery continues to be the gold standard therapy for dogs and cats diagnosed with MGT. The recommended surgical procedure varies between dogs and cats due to: 1) the chance of a malignancy across species (50% in dogs, > 90% in cats), and 2) the chance for recurrence with minimal excision (low in dogs, high in cats). Therefore, minimal excision via lumpectomy or mammaectomy is recommended for dogs with solitary MGT, whereas radical mastectomy is recommended for cats with MGT. A chain mastectomy should be considered in dogs only when

there are multiple lesions in a chain, as the chain mastectomy will be procedurally easier than multiple lumpectomy or mammaectomy. Considerations should be made in dogs and cats for axillary and inguinal LN dissection and histopathological examination with cranial and caudal gland MGT, respectively. In addition, considerations should be made for staged bilateral radical mastectomies in cats, especially those with better prognoses, as the chance for additional primary MGT that are malignant are extremely high. This is extremely controversial, but no different than the recommendations for prophylactic bilateral radical mastectomy in women with mutant breast cancer genes as the surgical procedure allows for early removal of multiple incipient disease areas for further cancer and potential metastasis can occur.

Additional therapies for dogs and cats with MGT exist, however, the clinical usefulness of these therapies is presently limited due to the paucity of studies presently available. For example, the use of chemotherapy as an adjuvant treatment of dogs with MGT is presently largely unexplored. Similarly, relatively few studies have explored the use of chemotherapy in cats with unresectable or metastatic MGT and no published studies are available to date concerning the adjuvant use of chemotherapy in cats with micro-metastatic MGT. A recently published study by Novosad and this author in a large series of cats with malignant MGT treated with 5 doses of doxorubicin after surgery found an approximate doubling of survival compared to historical controls published by MacEwen et al in 1984. The use of chemotherapy as an adjuvant treatment in dogs with high-risk MGT and cats with \geq Stage II MGT should be considered, however, the therapeutic efficacy of this approach remains to be determined. Palliative radiation therapy (large dose per fraction & relatively few fractions) can be considered for IMC and tumors that are extremely large and causing significant quality of life concerns. Biologic response modifiers have to date not been found to efficacious against MGT.

The effect of ovariectomy (OHE) at the time of primary tumor removal is presently extremely controversial. Three previous studies have found no effect; however, recent studies by Sorenmo et al and Chang et al have found an increase in survival for dogs that underwent OHE at the time of their primary MGT removal or \leq 2 years of the time of their primary MGT removal. At the very least, an OHE should be strongly considered in conjunction with the MGT resection to reduce the chance of subsequent pyometra; however, the effect of OHE on subsequent MGT and metastasis desperately needs further definitive study. The use of estrogen receptor blockers such as tamoxifen is also extremely controversial as separate studies show a pronounced anti-tumor effect and no effect, respectively. Tamoxifen usage is contraindicated in intact female dogs and cats due to pyometra, and the use of tamoxifen in spayed dogs and cats can result in stump pyometra, urinary tract infections, nesting behavior, etc. Since studies do not presently show documented clinical benefit in dogs and cats, their use on a routine basis is presently not recommended by this author.

Prognosis

The understanding of prognostic factors for dogs and cats with MGT is of paramount importance. These factors will help the clinician educate the client about their pet's prognosis and then direct questions and decisions about further therapy. The following factors are associated with a poor prognosis in dogs with MGT: 1) lymph node metastasis or other metastasis, 2) IMC, 3) carcino-sarcoma or ductular carcinoma, 4) high grade tumor and/or vasculo-lymphatic invasion, 5) \geq 3 cm. primary tumor, 6) invasive and/or fixed to underlying tissue, 7) high AgNOR count, 8) estrogen receptor negative, 9) ulceration, 10) lack of lymphoid cell reactivity, 11) increased microvessel density, 12) increased proliferation index scores

(AgNOR and Ki-67) and 13) increased VEGF expression. The following factors are associated with a poor prognosis in cats with MGT: 1) lymph node metastasis or other metastasis, 2) tumor size and stage (\geq 2-3 cm in diameter do worst), 3) higher grade tumors (poorly differentiated, increased mitotic figures, increased necrosis, etc.), 4) conservative surgery (vs. preferred radical mastectomy), 5) breed (Siamese & tricolor's do worse), 6) increasing age, 7) higher AgNOR counts, and 8) vasculo-lymphatic invasion. When dogs with MGT have poor prognostic factors as discussed above, this suggests they are at increased risk for metastasis and therefore adjuvant chemotherapy should be discussed with the client. While it is presently unknown which cats should have adjuvant chemotherapy, this author believes it should be strongly considered in most cats with malignant MGT since this is such an aggressive and metastatic malignancy.

MGT's are extremely common tumors in veterinary practice. The biologic heterogeneity seen with these tumors can be extreme; this underscores the need to have a greater understanding of the biology and prognostic factors of this disease. Surgery can be curative for approximately 75% of dogs with MGT, whereas cats with MGT generally have a poor prognosis. That said, the astute clinician when armed with an understanding of the biology and prognostic factors of dogs and cats with MGT, will be able to determine in advance the occasional situations where dogs have a poor prognosis MGT and when cats have a decent prognosis MGT and then counsel that client for the best therapies in each situation.

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