Proceeding of the NAVC
North American Veterinary Conference
Jan. 8-12, 2005, Orlando, Florida

SKIN TUMORS – CASE MANAGEMENT

William S. Dernell, DVM, MS, DACVS
College of Veterinary Medicine
Colorado State University, Fort Collins, CO

The skin is the most common location for tumors in the dog, representing 1/3 of all tumors seen. In the dog, the majority of skin tumors are benign (70-80%). The skin is the second most common site for tumor development in the cat, representing ¼ of all tumors seen. In the cat, the majority of skin tumors are malignant (50-65%). Some of the more common skin masses include; tumor-like lesions such as hyperplastic masses, papillomas, squamous cell carcinoma, basal cell tumor, sebaceous and sweat gland tumors, hair follicle tumors, melanoma, cysts and mast cell tumors.

The skin in both species is a possible, yet uncommon, site for metastatic disease. A number of predisposing factors are implicated with skin tumors including viruses, ionizing radiation, hormones, genetics, vaccines, heat and immunologic factors. Of all of these, the effect of ionizing radiation on the formation of skin tumors is the only factor that is well established. Ionizing radiation is implicated in the development of hemangioma and hemangiosarcoma in the dog as well as squamous cell carcinoma in the dog and cat.

The pathology of skin tumors is based on the tissue of origin broken down into epithelial, mesenchymal, melonotic or round-cell. They are then further subclassified by cell type (ex. squamous cell carcinoma, mast cell tumor, etc.). There is likely a continuum for most subtypes ranging from benign to malignant, rather than black and white differences between biologic behavior. Biologic behavior of many skin tumors can vary by location and by species (ex. mast cell tumor).

Animals are usually presented with a palpable and/or visible mass, which may become ulcerated or inflamed secondary to trauma. Historical perspectives can help discern benign from malignant skin masses such as; duration, growth rate, puritis and response to therapy. When evaluating skin masses it is important to record measurements (3 dimensions) and locations, especially if removal is not elected when the patient is first seen. This will assist in assessing historical changes over time.

A screening diagnostic test for any skin mass is a fine needle aspirate. This may yield a diagnosis, but in the least will help guide further diagnostics or treatment. Most skin tumors are treated similarly, with the notable exception of mast cell tumors, which can usually be differentiated by needle aspirate. For extremity or large lesions, lesions in difficult locations, or those highly suspected to be malignant, an incisional biopsy is warranted. This will invariably help with treatment planning. For small masses located on the trunk in well-skinned areas, an excisional biopsy may be reasonable. If, in fact, the lesion is malignant and further surgery required, such an excisional biopsy would not likely compromise the patient or the tumor control. Special stains or immunohistochemistry may help for equivocal histologic specimens. For suspected malignant lesions, staging to include cheat radiographs, aspiration of regional lymph nodes and possibly abdominal ultrasound is warranted, prior to definitive therapy. For suspected benign lesions, an excisional biopsy (if the lesion meets the criteria outlined above) may be performed and staging elected if the histology proves malignant.

The therapy for most skin masses is similar, the most notable exception being mast cell tumor, which is discussed in more detail below. Surgical excision is the treatment of choice for most skin masses. Adequate normal tissue margins must be obtained, as even benign masses incompletely excised will grow back. The amount of margin required is based on the biologic behavior of the tumor, which is assumed from history, physical appearance, needle aspirate or biopsy results. Conservative 1-2 cm margins in the skin surrounding the mass and deep margins below the subcutaneous tissue are usually adequate, even for more malignant skin tumors. If the initial resection is incomplete, the best choice for follow-up treatment is re-excision, if that is feasible. For larger lesions, cytoreductive surgery can be performed which is then followed by adjuvant treatment. Effective adjuvant treatments for most skin tumors include cryosurgery, radiation and photodynamic therapy. Chemotherapy may be indicated for malignancies although little data exists as to its efficacy. Retinoids (vitamin A derivatives) may have a positive effect for animals with multiple lesions or those predisposed to recurrent disease. Some evidence exists that retinoids may cause cells to differentiate into normal cells that will then undergo natural death, rather than undergo malignant transformation. Some support exists for their use in hemangioma/ hemangiosarcoma and squamous cell carcinoma. The prognosis for most skin tumors is excellent, with a good chance of cure following complete surgical removal.

MAST CELL TUMORS

Mast cell tumors (MCT) are the most common cutaneous tumor in the dog and the 2nd most common in the cat. Older names for MCT include mast cell sarcoma and histiocytic mastocytoma. Mast cell tumor must be differentiated from mastocytosis, which is a systemic mast cell condition. Mastocytosis can be seen in animals with MCT but is not common. In people, mastocytosis is seen, whereas mast cell tumors are not. Mast cells are normal inflammatory cells containing a variety of bioactive compounds, which are partially responsible for clinical syndromes seen with MCT. Histamine and heparin are the major constituents and cause the typical metachromatic staining on Wright stains. Some anaplastic lesions will not stain well and in these cases, immunohistochemistry may be helpful. Heparin, as well as proteolytic enzymes, present in mast cells can be responsible for hemorrhage from the surgery site as well as delay in wound healing. Histamine can cause local or systemic allergic-type reactions as well as gastric ulceration.

Mast cell tumors have a wide range of biologic behaviors, which can be partially predicted by histologic grade.

The standard grading scheme for MCT is divided into well differentiated (grade I), moderately differentiated (grade II) and undifferentiated (grade III). Grade I lesions are minimally invasive and do not metastasize. Grade II lesions are locally aggressive and invasive with a 10-20% rate of metastasis. Grade II lesions are locally invasive with a high (70-90%) rate of metastasis. Metastasis is typically to regional lymph nodes, liver, spleen or bone marrow.

Most MCT present as solitary masses. Low-grade tumors may be firm and have a lengthy duration. Higher-grade tumors may present with erythema, edema and/or ulceration. Manipulation of mast cell tumors can cause erythema and wheal formation (dariers sign) following mast cell degranulation. Metastasis can present locally or regionally (lymph node) or can be disseminated, involving

organomegally and mastocythemia. A fine needle aspirate is usually diagnostic for MCT, unless the mass is anaplasic (undifferentiated). Tumor grade cannot be determined from cytology, but requires histology. Agrophilic nucleolar organizer regions (AgNORs) are an indirect measurement of nuclear activity and correlate with tumor grade. Although not a test performed by all laboratories, AgNORs have the advantage of being able to be performed on cytology, as well as histology specimens. Full staging of the patient presenting for MCT is indicated, unless it is known that the lesion is grade I. Aspiration of any enlarged lymph nodes, abdominal ultrasound with spleen and liver aspiration and a bone marrow aspirate are indicated. The discovery of systemic disease has a major impact on prognosis and can greatly alter treatment planning. Evaluation of the buffy coat for mast cells is a simple screening step to look for mastocythemia, however, false negatives exist and a bone marrow aspirate is preferred. Indicators of mastocythemia can also be noted on complete blood count if basophilia or eosinophilia is seen. Biopsy, prior to tumor resection is indicated for larger lesions, extremity lesions or those in difficult locations. Tumor grade may well alter the treatment planning or the owner's willingness to treat in these cases. For small, trunk located lesions; an excisional biopsy may be reasonable if the need for re-resection (following incomplete initial resection) would not compromise the patient. In these cases, staging could be delayed until tumor grade is determined.

Surgical removal is the treatment of choice for local MCT disease. Grade II and III lesions warrant aggressive local resection, obtaining 3 cm lateral margins and one additional tissue margin deep to what the tumor touches. In certain areas, this type of resection will require some type of reconstructive procedure, or possibly a regional resection to be complete. Normal tissue margins should always be identified after removal so that the pathologist can assess the completeness of resection. In cases of incomplete resection, re-resection should be considered first if feasible. For re-resections, new margins are obtained as described above surrounding the old scar. Regional resection may also be re-considered. Complete surgical resection for dogs with no evidence of metastasis will result in upwards of 90% 1-year remission. For incomplete resection that is not amendable to surgery, radiation therapy to the site can be successful. Fractionated doses of approximately 50 Gy have resulted in 80-90% 1-year remissions.

For dogs with grade II tumors or evidence of metastatic disease, adjuvant chemotherapy should be considered. Although to date, no chemotherapy protocol has been proven efficacious, a combination protocol combining vinblastine, cytoxin and prednisone has shown some clinical responses. Previously evaluated drugs include cytoxin and vincrisine, which were not shown to be efficacious alone. Responses have also been seen following the use of doxorubricin, mitoxantrone and L-asparginase but are typically of short duration. Prednisone will consistently result in tumor response but the duration is short (30 days) and when used alone, it may induce drug resistance. Further evaluation of aggressive drug protocols may prove successful, however, to date, the overall survival for metastatic or grade III MCT is less that 6 months. Ancillary therapy for MCT may also be indicated, especially for disseminated disease. Histamine (H1 and/or H2) blockers are indicated for the prevention of allergic reactions and gastric ulceration. Gastrointestinal protectant agents may also be helpful in cases of suspected or confirmed ulceration.

Feline MCT generally behave in a less aggressive manner than in the canine. There are three distinct forms of MCT in the cat; mastocytic, histiocytic and visceral. The majority of cutaneous feline mast cells are mastocytic. Mastocytic MCT are further subtyped histologically into compact and diffuse. The most common subtype is diffuse, which behave very similarly to grade I MCT in the dog. Conservative surgical resection is generally curative. Diffuse mastocytic MCT tend to behave in a more aggressive manner, more similar to grade II or III MCT in the dog. Complete staging and aggressive treatment is indicated for the diffuse mastocytic form. Although the grading scheme for MCT in the dog does not apply to the cat, differentiation between compact and diffuse forms may help predict behavior and guide treatment planning.

Histocytic mast cell disease is most common in younger, Siamese cats. These cats usually present with multiple, inflamed, puritic lesions, which may actually spontaneously regress. This may be more of an allergic phenomenon than a true neoplasia. Biopsy is needed to differentiate this form from the mastocytic form. The visceral form of feline MCT can present isolated to the spleen or intestine, or can be diffuse. Splenic MCT will present with vague signs and splenomegaly. Up to 50% will have bone marrow involvement and coagulation abnormalities are not uncommon. Up to 30% can present with abdominal effusions. Intestinal MCT does not usually present with mastocythemia, but will often have evidence of regional metastasis to lymph nodes, liver or peritoneum. For MCT isolated to the spleen or intestine, complete resection can result in a long-term (approximately 1-year) remission. Cases presenting with metastatic disease carry a much more guarded prognosis. Chemotherapy protocols similar to the dog are presently being evaluated for diffuse mastocytic disease or visceral MCT with evidence of metastasis.

REFERENCE

1. Piscopo SE. Canine Mast Cell Tumors. Veterinary Forum, June 1999:32-41.