

A Review of Canine Mast Cell Tumor

*Rachel Reiman, DVM, DACVIM (Oncology)
Animal Emergency Center & Specialty Services*

Although mast cell tumors are the most common malignant skin tumor in the dog, the management of these cases can be very complicated and often frustrating due to the tremendous variability in biologic behavior of these tumors. Knowledge of the signs associated with a worrisome prognosis, and the steps to take to address the potential for recurrence and metastasis can help to simplify the approach to this common entity in small animal practice.

Mast cells are an important component to the immune system and are normal residents in a variety of tissues including the bone marrow, lymph nodes, skin, and spleen. These cells are thought to originate from a pluripotent hemopoietic stem cells within the bone marrow and then further differentiate in the tissues. Mast cells are responsible not only for type I hypersensitivity reactions but also play a role in many other inflammatory processes. Mast cells contain or produce substances that promote inflammation including histamine, serotonin, various proteolytic enzymes, heparin, prostaglandins, platelet activating factor, and various cytokines. Release of these substances leads to vasodilation, increased vascular permeability, bronchoconstriction, increased mucus production, and nerve stimulation among other processes. In mast cell tumors many of these substances are responsible for the local and systemic effects these tumors have on the patient.

Mast cell tumors are common - accounting for approximately 10-20% of all skin tumors in dog. The etiology of MCTs in dogs is largely unknown although recent evidence suggests that at least some tumors may be a result of mutant c-kit expression and/or p53. There are several breeds thought to be at increased risk for developing mast cell tumors and these include boxers, Boston terriers, Labrador retrievers, beagles, and schnauzers. It is important to note that the “breed” reported to developed MCT most commonly is the mixed breed dog. Although predisposed to the development of mast cell tumors boxers more commonly develop histologically low to intermediate forms of the disease, which tend to have a better prognosis. Most mast cell tumors develop in older dogs with a median of 9 years of age.

Canine MCT have been referred to as “ the great pretender” because they can look and feel like anything. They can be soft and subcutaneous (feeling exactly like a lipoma) or be firm and cutaneous (like a sebaceous cyst). Because of this characteristic, fine needle aspiration and cytology should be offered for any lump or bump encountered. Cytology for MCT is often rewarding as most mast cell tumors exhibit the classic appearance of a large population of round cells with abundant cytoplasm and the characteristic purple cytoplasmic granules. Diagnosis can usually be achieved in approximately 90% of dogs with FNA however in approximately 10% of MCTs the granules will not be present. It is not uncommon to see other leukocytes within the tumor such as eosinophils, basophils and neutrophils.

Once a presumptive diagnosis of MCT has been made, the next step is to attempt fine needle aspiration and cytology of the regional lymph node if possible. While the majority of canine MCT are locally aggressive, most are unlikely to metastasize so the question of staging the patient depends largely on several prognostic factors that have been recognized in prior studies. Identifying which tumors are more likely to metastasize can be helpful in distinguishing which patients are most likely to benefit from additional staging preoperatively. Prognostic factors for canine MCT are listed in Table 1. Since animals whose tumors display these criteria may have a higher likelihood of metastasis, a thorough search for disease elsewhere is indicated prior to undertaking expensive or aggressive definitive therapy. This may also be reasonable in lower-risk patients if very expensive or aggressive treatment is likely to be necessary, or if the tumor is in a location not amenable to wide surgical excision. In the absence of these factors, it is reasonable to proceed immediately to appropriately aggressive surgical excision.

Complete staging for canine MCT should include cytologic evaluation of the regional lymph node, abdominal ultrasound, thoracic radiographs, and bone marrow aspirate. Of these tests, abdominal imaging and lymph node cytology are the most likely to yield important results. Cytology of abnormal lymph nodes or organs in the abdomen is indicated, however aspirates of structurally normal liver and



spleen is rarely useful. If radical, expensive or potentially disfiguring surgery is being contemplated, an incisional biopsy may also be considered for histologic grading. If no evidence of disease elsewhere is found, appropriate local therapy can be pursued. Identification of disease in the regional lymph node means that this should be removed as well at the time of surgery, and that additional systemic therapy should be considered irrespective of histologic grade. Identification of disease beyond the regional lymph node usually means that surgery will be of little or no benefit.

SURGERY FOR MAST CELL TUMORS

Even well differentiated MCT are associated with aggressive local tissue infiltration. Thus, it is necessary to include a generous margin of normal-appearing tissue on all sides of the tumor (including underneath) to insure that any microscopic nests of tumor are removed. The standard recommendation is to remove a minimum of 3 cm of normal-appearing tissue 360 degrees around the tumor, and at least one normal fascial plane underneath. The entire specimen should be submitted in one piece, preferably with the margins inked, so that the pathologist can assess all margins for adequacy of excision. When necessary, very aggressive or radical surgical procedures, such as amputation or body wall resection, are reasonable to consider. Prior to contemplating procedure such as these, complete staging is essential, and incisional biopsy for determination of histologic grade is helpful. When dealing with a low or intermediate-grade tumor, very aggressive surgery is reasonable because the likelihood of metastasis is small.

INTERPRETING THE PATHOLOGY REPORT

Two equally important pieces of information need to be gleaned from the pathology report: (1) Histologic grade; and (2) Adequacy of surgical margins. If only a representative piece of the tumor is submitted, margins cannot be evaluated and the utility of the report is cut in half. Pathologists often utilize a numeric grading scheme, where “Grade I” is well-differentiated and “Grade III” is poorly differentiated, however some pathologists will now utilize words such as “low, intermediate or high-grade” or “well, poorly or intermediately differentiated” in place of a numerical scale. If information regarding grade or margins is not provided, it should be requested from the pathologist.

Low or intermediate grade cutaneous MCT with complete surgical margins usually require no further therapy, as the risk of recurrence or spread is only approximately 5%. However, regular rechecks for recurrence, metastasis, or new cutaneous masses is indicated. Low or intermediate grade tumors with incomplete surgical margins have a high chance of recurrence, but a low chance for metastasis. Thus, further aggressive local therapy is reasonable. When possible, immediate re-excision of the surgical scar (and an additional 3 cm tissue in all directions and another fascial plane deep) is the most useful treatment. The entire excised tissue should be inked and re-submitted for histopathology. When this is not possible, the next best option would be the use of radiotherapy. Chemotherapy may be useful to prevent recurrence in cases where additional surgery or radiotherapy is not possible or has been declined.

High grade MCT with complete surgical margins has a low chance for recurrence, but a high chance for eventual metastasis. Systemic therapy (e.g. chemotherapy) can be offered in an attempt to delay or prevent this. High grade MCT with incomplete margins has a high likelihood of both recurrence and metastasis: Therapy designed to address both of these possibilities (e.g. additional surgery or radiotherapy, with chemotherapy) is indicated.

CAUTION OWNERS AGAINST A “WAIT AND SEE” APPROACH

The importance of addressing the potential for local recurrence the very first time the tumor appears cannot be overstated. Owners should be strongly cautioned against adopting a “wait and see” posture, with the intent of becoming more aggressive if/when the tumor grows back. Recurrent tumors are likely to grow more quickly, invade more deeply, and are more likely to ulcerate or become painful. In a recent study, dogs with MCT that were locally recurrent at the time aggressive therapy was started were more than 4 times more likely to die as a result of MCT than dogs that started aggressive therapy at the



first occurrence.

RADIOTHERAPY

Incompletely excised MCT of any grade have a high likelihood for local recurrence. As was discussed earlier, recurrent MCT have a much worse prognosis, even with aggressive therapy. For those tumors where appropriate aggressive surgery is not possible, several other local therapeutic modalities have been investigated for the adjuvant treatment of canine MCT. Radiotherapy (RT) has proven to be a very effective local treatment modality when utilized after incomplete surgical excision. Two-year control rates of 85 to 90% can be expected when incompletely excised low- or intermediate-grade MCT are treated with RT. Radiotherapy to bulky tumors is consistently less effective than RT to microscopic disease, with a one-year control rate of approximately 50%. The RT protocol currently in use at most radiation facilities for incompletely resected, low-or intermediate-grade MCT consists of a total of 15 treatments, given Monday through Friday for 3 weeks. Each treatment requires a very brief general anesthesia, which is typically very well tolerated. As a local form of therapy, there are no systemic side effects from RT. However, pets can develop varying degrees of acute hyperemia, pruritus and moist dermatitis at the RT site. This typically starts the third week of treatment, and resolves within 2-4 weeks. The RT site may be permanently alopecic, or may have hair of a different color. Overall, RT is exceptionally well tolerated by most animals.

CHEMOTHERAPY

MCT of low or intermediate histologic grade (Histologic Grade I or II) comprise 60 to 80% of all cutaneous MCT in the dog. These tumors exhibit quite aggressive local tissue invasion, necessitating aggressive local therapy to prevent recurrence. However, their metastatic rate is relatively low. High-grade or undifferentiated MCT (Grade III), in addition to being very locally infiltrative, have a considerably higher metastatic rate. Thus, aggressive surgery or other local therapies, while still necessary, are considered insufficient for optimum control. The presence of these highly metastatic undifferentiated tumors, and their high potential for metastasis, have prompted the search for other effective treatment modalities.

Animals with undifferentiated MCT, MCT that have metastasized, or tumors in a historically unfavorable location may benefit from the addition of some form of systemic therapy to appropriate local therapy. In addition, aggressive surgery or RT may be cosmetically unappealing or financially impossible for some owners. Several studies have been published investigating various systemic therapies for measurable canine MCT. By far the most commonly used chemotherapy protocol for MCT is a protocol using prednisone and vinblastine.

- ❖ Prednisone and vinblastine administration - Prednisone is administered orally at an initial dose of 2 mg/kg SID, and this dose is tapered and discontinued over approximately 3 months. VBL is given as a rapid intravenous bolus at 2-3 mg/m² every 1-2 weeks. The standard protocol consists of weekly injections for 4 weeks, followed by 4 biweekly injections.
- ❖ Side Effects - Adverse effects are noted in approximately 20% of patients, usually after the first dose of VBL. These are mild in most. Mild side effects include self-limiting vomiting, neutropenia without evidence of sepsis (7-day neutrophil count less than 1,000/ μ L), or lethargy/soft stool. Severe side effects occur in only approximately 5% of patients.
- ❖ Efficacy - As an adjuvant therapy to incomplete surgical resection (“microscopic disease”), VBL and prednisone treatment conferred a 57% one and two-year disease free rate. Although this is less than the 85 to 90% two-year disease free rate conferred by



surgery plus RT, this number represents a significant improvement over incomplete resection alone. It should be pointed out that this represents a small case number, and results may vary with a larger sampling of “microscopic disease” patients. As adjuvant therapy to prevent metastasis in patients with “high-risk” disease (i.e. high grade tumor, lymph node metastasis, historically unfavorable location), prednisone and vinblastine results in 2-year disease-free survivals of 60%. Interestingly, there seems to be a profound difference between the outcome of a high-grade tumor and an intermediate-grade tumor with lymph node metastasis. Despite the presence of lymph node metastasis, 90% of patients with grade II tumors with positive lymph nodes are disease-free at two years. Patients with grade III tumors treated in the adjuvant setting have 2-year survival rates of 60%. This appears to be a significant improvement over historical data employing surgery alone, which report 3-year survivals of less than 15%.

NEW DIRECTIONS

One of the most important recent findings with potential to translate into new and exciting forms of therapy is the discovery that the majority of canine mast cell neoplasms express alterations in the expression of, or genetic mutations within, the gene that encodes the tyrosine kinase growth factor receptor c-kit. This gene codes for a transmembrane protein that serves as the receptor for the hormone stem cell factor, important in the maturation of normal mast cells and other hematopoietic cells. It has been shown that the majority of canine MCT either aberrantly express c-kit or contain mutations that render c-kit constitutively active in the absence of bound stem cell factor. In other words, these mutations mean that the cells are receiving signals to proliferate and survive when they normally would not, leading to unchecked growth. New molecules have been developed that inhibit signaling through the c-kit tyrosine kinase, and there is now information that some of these compounds are able to interfere with the proliferation of canine MCT in vitro, and have shown great promise in preliminary evaluation in canine patients with MCT.

SUMMARY

Combination chemotherapy with prednisone and vinblastine appears to be an effective therapy for canine MCT. In addition to apparently increasing the survival time of high-risk (grade III) patients after surgery, it may also be beneficial for animals with incompletely resected intermediate grade tumors where aggressive local therapy (surgery, RT) is not possible or has been declined. The cost of these drugs is relatively low, particularly in comparison to RT, and they appear to be well tolerated by the majority of canine patients. It is important to remember that, while radiotherapy and chemotherapy are potentially very useful adjuvant forms of therapy, aggressive surgery remains the mainstay of treatment for canine MCT, and is sufficient to successfully treat the majority of MCT encountered in practice.



Table 1.

Prognostic variable	Explanation	Reference
Histologic grade	This is one of the strongest prognostic variables. Three-year survival rates - Grade I - 90%; Grade II - 55%; Grade III - 10-15%.	Meuten, D.J. (2002) Tumors in Domestic Animals. Iowa State Press, AMES, IA.
Clinical stage	Dogs with tumors confined to the skin with no evidence of distant disease have a better prognosis compared to dogs with lymph node or systemic metastasis	Gerritsen RJ, Teske E, Kraus JS et al: Multiagent chemotherapy for mast cell tumours in the dog, Vet Q 20:28-31, 1998. Bostock DE: The prognosis following surgical removal of mastocytomas in dogs, J Small Anim Pract 14:27-40, 1973. Ayl RD, Couto CG, Hammer AS et al: Correlation of DNA ploidy to tumor histologic grade, clinical variables, and survival in dogs with mast cell tumors, Vet Pathol 29:386-390, 1992 Turrel JM, Kitchell BE, Miller LM et al: Prognostic factors for radiation treatment of mast cell tumor in 85 dogs, J Am Vet Med Assoc 193:936-940, 1988.
Location	Locations such as: Inguinal area, oral, other mucocutaneous sites, and subungual have a worse prognosis.	Moriello KA, Rosenthal RC: Clinical approach to tumors of the skin and subcutaneous tissues, Vet Clin N Am Small Anim Pract 20:1163-1190, 1990. O'Keefe DA: Canine mast cell tumors, Vet Clin N Am Small Anim Pract 20:1105-1115, 1990. Richardson RC, Rebar AH, Elliott GS: Common skin tumors of the dog: a clinical approach to diagnosis and treatment, Comp Cont Ed Pract Vet 6:1080-1086, 1984. Turrel JM, Kitchell BE, Miller LM et al: Prognostic factors for radiation treatment of mast cell tumor in 85 dogs, J Am Vet Med Assoc 193:936-940, 1988. Sfiligoi G, Rassnick KM, Scarlett JM et al: Outcome of dogs with mast cell tumors in the inguinal or perineal region versus other cutaneous locations: 124 cases (1990-2001), J am Vet Med Assoc 226:1368-1374, 2005.
Growth rate	Stable tumors present for prolonged periods of time tend to be less aggressive	Bostock DE: The prognosis following surgical removal of mastocytomas in dogs, J Small Anim Pract 14:27-40, 1973.
Systemic signs	Dog with systemic illness (vomiting, anorexia, melena, etc) have a worse prognosis	Mullins MN, Dernell WS, Withrow SJ et al: The syndrome of multiple cutaneous canine mast cell tumors: 54 cases (1998-2004), J am Vet Med Assoc 228:91-95, 2006. Pollack MJ, Flanders JA, Johnson RC: Disseminated malignant mastocytoma in a dog, J Am Anim Hosp Assoc 27:435-440, 1991. O'Keefe DA: Canine mast cell tumors, Vet Clin N Am Small Anim Pract 20:1105-1115, 1990.
Recurrence	Local regrowth of a tumor is associated with a poorer prognosis	Thamm DH, Mauldin EA, Vail DM: Prednisone and vinblastine chemotherapy for canine mast cell tumor: 41 cases (1992-1998) J Vet Intern Med 13:491-497, 1999.

