

MAST CELL TUMORS: TO CUT OR NOT TO CUT

C. Guillermo Couto, DVM, Dip. ACVIM
Couto Veterinary Consultants
Hilliard, OH 43026
coutovetconsultants@gmail.com

Not one of them is like the other, don't ask me why, please ask your mother.

From *One Fish, Two Fish, Red Fish, Blue Fish* by Dr. Seuss

Mast cell tumors (MCTs) are one of the most common skin tumors in dogs and are relatively common in cats. They originate from mast cells, which are intimately involved in the local control of vascular tone and which contain a large array of intracytoplasmic bioactive molecules, including heparin, histamine, leukotrienes, and several cytokines. Given their unpredictable biologic behavior, the term *mast cell tumor* is preferred to *mastocytoma* or *mast cell sarcoma*. Because of differences in the clinical and pathologic features of canine and feline MCTs, they are discussed separately.

MAST CELL TUMORS IN DOGS

Etiology and Epidemiology

MCTs constitute approximately 20% to 25% of the skin and subcutaneous tumors seen by practicing veterinarians. Brachiocephalic breeds (Boxer, Boston Terrier, Bull Mastiff, English Bulldog) are at high risk for MCTs. These tumors are also more common in middle-aged to older dogs (mean age, approximately 8.5 years) than in younger dogs, but there is no gender-related predilection. MCTs have been found in sites of chronic inflammation or injury, such as burn scars.

Clinical and Pathologic Features

MCTs occur either as dermoepidermal masses (i.e., a superficial mass that moves with the skin) or subcutaneous masses (i.e., the overlying skin moves freely over the tumor). Grossly, MCTs can mimic any primary or secondary skin lesion, including a macula, papula, nodule, tumor, and crust. Approximately 10% to 15% of all MCTs in dogs are clinically indistinguishable from the common subcutaneous lipomas. As a rule, an MCT cannot be definitively diagnosed until the lesion has been evaluated cytologically or histopathologically.

Most MCTs are solitary, although multifocal MCTs can occur in dogs. Regional lymphadenopathy caused by metastatic disease is also common in dogs with invasive MCTs. Occasionally splenomegaly or hepatomegaly is present in dogs with systemic dissemination.

Given the fact that mast cells produce a variety of bioactive (mainly vasoactive) substances, dogs with MCTs may be evaluated because of diffuse swelling (i.e., edema and inflammation around a primary tumor or its metastatic lesion), erythema, or bruising of the affected area. These episodes may be acute, and they may occur during or shortly after exercise or exposure to cold weather. Percutaneous FNA of an

unexplained subcutaneous swelling in dogs should always be performed as part of the work-up.

A “typical” MCT is a dermoepidermal, dome-shaped, alopecic, and erythematous lesion. However, as discussed in previous paragraphs, MCTs rarely have a typical appearance. A clinical feature that may aid in the diagnosis of an MCT is Darier’s sign, which is the erythema and wheal that form after the tumor is slightly traumatized (i.e., scraped or compressed).

Most dogs with MCTs have a normal CBC, although eosinophilia (sometimes marked), basophilia, mastocytosis, neutrophilia, thrombocytosis, or anemia, or a combination of these, may be present. Serum biochemistry abnormalities are uncommon.

From a histopathologic standpoint, MCTs are traditionally classified into three categories: well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3). Several studies have shown that dogs with grade 1 tumors treated with surgery or radiotherapy have longer survival times than identically treated dogs with grade 3 tumors, mainly because well-differentiated neoplasms have a lower metastatic potential (i.e., most tumors in dogs with systemic mast cell disease are grade 3). Special stains may be required to identify the typical intracytoplasmic granules in poorly differentiated neoplasms. The mitotic index is of prognostic relevance in dogs with MCTs, so it should be provided by the pathologist. In addition to the grading of the tumor, the pathologist should provide the clinician with information regarding the completeness of the excision. A dog with an incompletely excised MCT is rarely cured by the initial surgical procedure and requires either a second surgery or irradiation of the affected area.

From a molecular standpoint, a variable percentage of canine MCTs have c-kit mutations; c-kit is the stem cell growth factor receptor, and its mutation results in immortalized clones that do not undergo apoptosis.

Biologic Behavior

The biologic behavior of canine MCTs can be summed up in one word: unpredictable. Even though several criteria may help in establishing the biologic behavior of these neoplasms, they rarely apply to an individual dog (i.e., they may be meaningful from the statistical viewpoint).

In general, well-differentiated (grade 1), solitary cutaneous MCTs have a low metastatic potential and low potential for systemic dissemination. However, one may encounter a dog with several dozen cutaneous MCTs, which on histopathologic evaluation are well differentiated.

Grade 2 and 3 tumors have a higher metastatic potential and a higher potential for systemic dissemination than grade 1 MCTs. Metastases to the regional lymph nodes commonly occur (particularly in dogs with grade 3 tumors), although occasionally a tumor “skips” the draining lymph node and metastasizes to the second or third regional node (e.g., a digital MCT in the rear limb metastasizing to the iliac or sublumbar node). Nodal metastases can be present in normal sized lymph nodes, so we routinely aspirate every lymph node in the region of a MCT, independently of whether it is enlarged or not. Pulmonary metastases are extremely rare. Although not evident from published clinical

data, it appears that MCTs in certain anatomic locations are more aggressive than tumors in other areas. For example, distal limb (e.g., toe), perineal, inguinal, and extracutaneous (e.g., oropharyngeal, intranasal) MCTs appear to have a higher metastatic potential than similarly graded tumors in other regions (e.g., trunk, neck).

Another biologic characteristic of canine MCTs is that they may become systemic, behaving like a hematopoietic malignancy (i.e., a lymphoma or leukemia). These dogs usually have a history of a cutaneous MCT that was excised. Most dogs with systemic mast cell disease (SMCD) are evaluated because of lethargy, anorexia, vomiting, and weight loss in association with splenomegaly, hepatomegaly, pallor, and, occasionally, detectable cutaneous masses. The CBC in affected dogs commonly reveals cytopenias, with or without circulating mast cells.

MCTs can release bioactive substances that may cause edema, erythema, or bruising of the affected area. Gastrointestinal tract ulceration may also occur as a result of hyperhistaminemia (approximately 80% of dogs euthanized because of advanced MCTs have gastroduodenal ulceration). Therefore any dog with an MCT should undergo occult fecal blood testing. Profuse intraoperative and postoperative bleeding and delayed wound healing occur in some dogs as a consequence of the bioactive substances released from mast cells.

Diagnosis

The evaluation of a dog with a suspected MCT should include FNA of the affected area. MCTs are extremely easy to diagnose cytologically. They consist of a monomorphic population of round cells with prominent intracytoplasmic purple granules; eosinophils are frequently present in the smear. In approximately one-third of MCTs, the granules do not stain with Diff-Quik; hence, if agranular round cells are found in a dermal or subcutaneous mass resembling an MCT, the clinician should stain the slide with Giemsa or Wright's stain to reveal the characteristic purple granules. A cytologic diagnosis of MCT allows the clinician to discuss treatment options with the owner and to plan therapeutic strategies.

Although clinical pathologists will frequently state the degree of differentiation of the cells in a cytologic specimen of an MCT, that scheme does not necessarily correlate with the histopathologic grading system. In other words, a cytologic diagnosis of a well-differentiated MCT does not necessarily imply that it will be a grade 1 tumor when evaluated histopathologically (i.e., cytologic grading may not have the same prognostic implications as histopathologic grading).

The clinical evaluation of a dog with a cytologically confirmed MCT should include careful palpation of the affected area and its draining lymph nodes; abdominal palpation, radiography, or ultrasonography to search for hepatosplenomegaly; a CBC, serum biochemistry profile, and urinalysis; and thoracic radiography if the neoplasm is in the anterior one-half of the body (i.e., to detect intrathoracic lymphadenopathy). If lymphadenopathy, hepatomegaly, or splenomegaly is present, FNA of the enlarged lymph node or organ should be performed to detect mast cells (i.e., local neoplasm versus metastatic tumor versus SMCD).

The use of a buffy coat smear to search for circulating mast cells is controversial. It was thought that the presence of mast cells in a buffy coat smear indicated systemic dissemination and therefore a poor prognosis. However, dogs with a solitary, potentially curable MCT occasionally have low numbers of circulating mast cells that disappear from circulation shortly after the primary tumor is excised or irradiated. Moreover, a recent study revealed that circulating mast cells are more common in dogs with diseases other than MCTs; over 95% of the CBCs with circulating mast cells were from dogs with inflammatory disorders, regenerative anemia, tumors other than MCTs, and trauma. Also, dogs with MCT had significantly lower circulating mast cell counts (71 per buffy coat smear) than those with other diseases (276 per buffy coat smear). Cytologic evaluation of a bone marrow aspirate may therefore be more beneficial for staging purposes. Dogs with more than five mast cells per 500 nucleated cells are believed to have SMCD; however, bone marrow mast cells have also been documented to disappear after excision or irradiation of the primary tumor. Therefore there is disagreement as to the appropriate staging procedures in dogs with MCTs. At our clinic we do not use buffy coat smears or bone marrow aspirates routinely in dogs with MCT and a normal CBC; if cytopenias or leukoerythroblastic reactions are present, we perform a bone marrow aspirate.

As discussed previously, all dogs with MCTs should be tested for occult blood in the stool even if melena is not evident. There are several kits for this purpose. The presence of blood in the stool is suggestive of upper gastrointestinal tract bleeding. If this is found on repeat testing, the dog should be treated with H₂ antihistamines (i.e., famotidine, ranitidine) with or without a coating agent (i.e., sucralfate). Once this clinical information is obtained, the tumor should be staged to determine the extent of disease (Table 1).

Treatment and Prognosis

As discussed previously, it is imperative to know whether the mass the clinician is preparing to excise is an MCT, because this information is useful when discussing treatment options with the client and when planning the treatment strategy. Dogs with MCT can be treated with surgery, radiotherapy, or chemotherapy or a combination of these. However, the first two treatment options are potentially curative, whereas chemotherapy is usually only palliative. Treatment guidelines are provided in Table 2.

A solitary MCT in an area in which complete surgical excision is feasible should be removed by aggressive en bloc resection (i.e., 2-3 cm margins around and underneath the tumor). If a complete excision is obtained (according to the pathologist evaluating the specimen), the tumor is grade 1 or 2, and no metastatic lesions are present, there is usually no need for further treatment (i.e., the dog is most likely cured). If the excision appears incomplete, the clinician can take one of three courses of action: (1) perform a second surgery in an attempt to excise the remaining tumor (the excised area should be submitted for histopathologic evaluation to assess the completeness of excision); (2) irradiate the surgical site (35 to 40 Gy delivered in 10 to 12 fractions); or (3) administer a short course (3-6 months) of lomustine chemotherapy (see below). The three options appear to be equally effective, resulting in approximately 80% probability of long-term survival.

A solitary MCT in an area in which surgical excision is difficult or impossible, or at a site where the cosmetic or functional results are unacceptable (e.g., prepuce, eyelid), can be successfully treated with radiotherapy. Approximately two-thirds of dogs with a grade 1 or 2 localized MCT treated with radiotherapy alone are cured. Irradiation is also recommended for the management of tumors in “high-risk” areas. Intralesional injections of corticosteroids (triamcinolone [Vetalog], 1 mg intralesionally per centimeter of tumor diameter every 2 to 3 weeks) can also successfully shrink the tumor (although it is usually only palliative). Intralesional injections of deionized water have also been reported to be beneficial in managing local MCTs, although that has not been my experience. An alternative approach is to use neoadjuvant chemotherapy (ie; chemotherapy before and after surgery). In these dogs, we combine lomustine and prednisone, with or without vinblastine, in order to decrease the tumor size; then we do surgery, and continue with chemotherapy to “clean up” the area (see below).

Once metastatic or disseminated MCTs (or SMCD) develop, a cure is rarely obtained. Treatment in these dogs consists of chemotherapy and supportive therapy and is aimed at palliating the neoplasm and its complications. Results of prospective studies of chemotherapy in dogs with MCTs have not been very encouraging; two chemotherapy protocols have been widely used: (1) prednisone and (2) the CVP protocol (cyclophosphamide, prednisone, vinblastine). Over the past several years, lomustine (CCNU) has been used with a high degree of success in dogs with nonresectable, metastatic, or systemic MCTs. The probability of response is high (>50%), and we have documented remissions in excess of 18 months in dogs with metastatic grade 2 and 3 MCTs. Lomustine can be combined with prednisone, vinblastine, or both (Table 3).

Traditionally, I used lomustine, with or without prednisone (see Table 3), and famotidine and/or sucralfate, in dogs with metastatic or nonresectable MCTs. Although lomustine is potentially myelosuppressive, clinically relevant cytopenias are rare; however hepatotoxicity is common, so chemistry profiles should be evaluated periodically. The addition of vinblastine allows administration of lomustine every 6 weeks instead of every 3 weeks; this may decrease the prevalence of hepatotoxicity.

Small molecule tyrosine kinase inhibitors have demonstrated efficacy against some canine MCTs with c-kit mutations, and are currently available (toceranib and masitinib). For dosing information on Palladia (toceranib) see Table 3.

MAST CELL TUMORS IN CATS

Etiology and Epidemiology

Although MCTs are relatively common in cats, they rarely result in the considerable clinical problems seen in dogs with this neoplasm. Most cats with MCTs are middle-aged or older (median, 10 years old), there is apparently no gender-related predilection, and Siamese cats may be at high risk. Feline leukemia virus and feline immunodeficiency virus do not play a role in the development of this tumor.

As opposed to the dog, in which most of the MCTs are cutaneous or subcutaneous, there are two main forms of feline MCTs: visceral and cutaneous. There is controversy as to whether cutaneous forms are more common than visceral forms and whether both forms can coexist in the same cat. At our clinic the cutaneous form is considerably more

common than the visceral form, and it is extremely rare for the cutaneous and visceral forms to coexist.

Clinical and Pathologic Features

Visceral MCTs are characterized by either hemolymphatic or intestinal involvement. Cats with hemolymphatic disease are classified as having SMCD (or mast cell leukemia), because the bone marrow, spleen, liver, and blood are commonly involved. Most cats initially have nonspecific signs, such as anorexia and vomiting; abdominal distention caused by massive splenomegaly is a consistent feature. As in dogs, the hematologic abnormalities in cats with SMCD are extremely variable and include cytopenias, mastocytosis, basophilia, or eosinophilia, or a combination of these; however, a high percentage of cats may have normal CBCs. Cats with the intestinal form of SMCD usually are evaluated because of gastrointestinal signs such as anorexia, vomiting, or diarrhea. Abdominal masses are palpated in approximately one-half of these cats. Most tumors involve the small intestine, where they can be solitary or multiple. Metastatic disease affecting the mesenteric lymph nodes, liver, spleen, and lungs is commonly found at the time of presentation. Multiple intestinal masses in cats are most commonly associated with lymphoma and with MCT, although both neoplasms can coexist. Gastrointestinal tract ulceration has also been documented in affected cats.

Cats with cutaneous MCTs usually initially have solitary or multiple, small (2 to 15 mm), white to pink, dermoepidermal masses primarily in the head and neck regions, although solitary dermoepidermal or subcutaneous masses also occur in other locations. It has been reported that, on the basis of the clinical, epidemiologic, and histologic features, MCTs in cats can be classified as either mast cell–type MCTs (common) or histiocytic–type MCTs (rare). Cats with mast cell–type MCTs are usually more than 4 years of age and have solitary dermal masses; there is no apparent breed predilection. Cats with histiocytic–type MCTs are primarily Siamese cats under 4 years of age. Typically such cats have multiple (miliary) subcutaneous masses that exhibit a benign biologic behavior. Some of these neoplasms appear to regress spontaneously. We have never seen the histiocytic type of disease in cats treated at our clinic, even in Siamese cats with multiple dermoepidermal nodules. The subcutaneous MCTs commonly seen in dogs are extremely rare in cats. Unlike the situation in dogs, the histopathologic grade does not appear to correlate well with the biologic behavior of MCTs in cats.

Diagnosis and Treatment

The diagnostic approach to cats with MCT is similar to that in dogs. As in dogs, some mast cells in cats are poorly granulated and the granules may not be easily identified during a routine cytologic or histopathologic evaluation.

The treatment for cats with MCTs is controversial. As a general rule, surgery is indicated for cats with a solitary cutaneous mass, for cats with two to five skin masses, and for cats with intestinal or splenic involvement. As discussed above, cutaneous MCTs in cats are less aggressive than in dogs, and in a large proportion of cats, removal of a solitary dermoepidermal MCT using a biopsy punch is curative; the same applies to cats with fewer than five dermoepidermal MCTs. The combination of splenectomy, prednisone, and chlorambucil (leukeran) treatment is recommended for

cats with SMCD, in which survival times in excess of approximately 1 year are common; splenectomy alone does not result in prolonged survival. Surgical excision and prednisone treatment are recommended for cats with intestinal MCT. Prednisone alone (4 to 8 mg/kg PO q24-48h) may also be beneficial for cats with systemic or metastatic MCTs. Cats with multiple skin MCTs are best treated with prednisone, in the dosage just given. Although radiotherapy is as effective in cats as in dogs, it is rarely necessary in cats with this neoplasm. When an additional chemotherapeutic agent is needed in cats with MCTs, I usually use chlorambucil (Leukeran, 20 mg/m² PO q2wk); this drug seems to be quite effective and well-tolerated. In my limited experience, lomustine (CCNU) is not very effective in cats with MCTs.

Table 1: Clinical Staging Scheme for Dogs with Mast Cell Tumors

Stage Description

- I One tumor confined to the dermis without regional lymph node involvement
 - a. Without systemic signs
 - b. With systemic signs
- II One tumor confined to the dermis with regional lymph node involvement
 - a. Without systemic signs
 - b. With systemic signs
- III Multiple dermal tumors or a large infiltrating tumor with or without regional lymph node involvement
 - a. Without systemic signs
 - b. With systemic signs
- IV Any tumor with distant metastases or recurrence with metastases
 - a. Without systemic signs
 - b. With systemic signs

Table 2: Treatment Guidelines for Dogs with Mast Cell Tumors

STAGE	GRADE	RECOMMENDED TREATMENT	FOLLOW-UP
I	1, 2	Surgical excision	Complete: observe Incomplete: second surgery or radiotherapy; chemo?
I	3	Chemotherapy*	Continue chemo
II	1, 2, 3	Surgical excision or radiotherapy	CCNU and prednisone *
III, IV	1, 2, 3	Chemotherapy*	Continue chemo

Table 3: Chemotherapy protocols for dogs with mast cell tumors:

1. Prednisone, 50 mg/m² by mouth (PO) q24h for 1 week; then 20-25 mg/m² PO q48h indefinitely plus lomustine (CCNU, Ceenu), 60 mg/m² PO q3wk.
2. Prednisone, 50 mg/m² by mouth (PO) q24h for 1 week; then 20-25 mg/m² PO q48h indefinitely plus lomustine (CCNU, Ceenu), 60 mg/m² PO q6wk, alternating doses with vinblastine, 2 mg/m², IV, q6wk (the dog receives lomustine, 3 weeks later vinblastine, 3 weeks later lomustine again, and so on)
3. Toceranib (Palladia) 2.2-2.7 mg/kg, PO, on Mon, Wed, Fri; gastroprotectants should be used in conjunction with Palladia.