Mast Cell Disease
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Normal mast cells are of hematopoietic origin and function as mediators of IgE specific inflammatory and hypersensitivity responses. Granules in the mast cells contain a number of vasoactive substances, including heparin and histamine, which induce the typical mast cell degranulation reaction of redness, pain, swelling, and itch. Malignant transformation of mast cells is a rare event in human beings but unfortunately a common event in dogs and to a lesser extent cats. Because the species in which the molecular pathogenesis of cancer is usually studied (humans) is not much affected by this disorder, research regarding the underlying cause of this disorder is scant. There is clearly a breed predisposition in mast cell disease, suggesting a genetic contribution. Environmental carcinogenesis for mast cell disease has not been well studied.

Etiopathogenesis of canine cutaneous mast cell tumors - Canine cutaneous mast cell tumors (MCT) are a challenge for the veterinarian. Tumors occur in older dogs (mean age 9 years), but any age may be affected. There is no sex predisposition. Flat nosed English breeds (Boxers, Boston terriers, Bullmastiff's) have a hereditary predisposition. Shar Pei's appear to be prone to a particularly aggressive variant. Boxers and possibly golden retrievers tend to have well-differentiated tumors, according to some authors. Other breeds at risk include Labrador retrievers, cocker spaniels, and schnauzers. While the exact etiology of canine mast cell tumors remains unknown, several factors have been implicated over the years. An early study suggested a viral etiology, based on the observation of apparent cell-free transmission of mast cell disease in experimental dogs. No infectious etiologic agent has ever been identified, however. The role of genetic factors and exposure to environmental carcinogens is probable. London et al and other investigators identified mutations in the proto-oncogene c-kit, which is the receptor for hematopoietic stem cell factor, in canine MCTs. These mutations consist of internal tandem duplications in the negative regulatory juxtamembrane domain of kit. It is estimated that these tandem duplication mutations exist in 38% of canine mast cell cases, and is associated with more aggressive biologic behavior and higher tumor grade. These mutations result in constitutive activation of the gene, causing the cells to divide inappropriately, ultimately resulting in a tumor. Another less well-explored mutation is a deletion at intron 11 of the c-kit gene, which is adjacent to the exon which codes for the juxtamembrane domain, in 49% of MCT. The role of c-kit mutations in canine mast cell tumors is being actively explored, as receptor tyrosine kinase inhibitors are a class of drugs tailored to inhibit aberrant signaling through pathways such as c-kit. Thus, dogs with spontaneous mast cell tumor could benefit from drug discoveries, and dogs also provide a useful preclinical model for drug development for humans with cancer.

Staging - Staging for mast cell tumors involves grading the local tumor and assessing regional lymph node and distant sites such as liver and spleen. In the dog, 50% of MCT are benign and cured by surgery. However, an additional 50% are malignant. Malignant mast cell tumors can recur locally or can become metastatic, with the higher histologic grades of tumor associated with more aggressive behavior. Historically, the published literature and text references recommend that mast cell patients be staged with
thus, III grade MI mitotic per 10 high power fields (400x) had a median survival time of 18 months, vs. dogs with >7 predict proliferative period with in high-grade tumors (J Comp Path 2007 136(4):231-9). 1199 the MCT. MCT higher muzzle those in in the liver and spleen involvement, and bone marrow aspiration yielded less that 2% positive results in a large series of more than 100 cases. These recommendations have not been uniformly accepted throughout the veterinary oncology community, however. More recently, a 5 year retrospective ultrasound study from Tufts revealed that in 19 patients, mast cell tumors may be detected in the abdominal cavity as organomegaly, diffuse hyperechoic lesions, focal hypoechoic lesions, or the liver and spleen may be completely unremarkable sonographically and yet still yield mast cell disease on cytology. Feline mast cell disease might be detected as thickening at the ileoceccolic junction or loss of intestinal wall layering. Mast cell tumors that are destined to become metastatic are generally the Grade III tumors.

**Prognostic factors** - Prognostic factors include the location of the primary tumor, in that tumors of the inguinal, axillary, and perineal region may be more aggressive than those arising on the lateral trunk, head or extremities. Mast cell tumors that arise in the muzzle in the dog are reported to be more aggressive than those at other locations, with higher regional metastatic rates than reported for MCT at other sites. Studies suggest that MCT located in the subcutaneous tissues, as compared to intradermal or muscle invasive MCT. In 53 cases of SQ mast cell tumors, margins were considered incomplete in 66% of the cases, and metastasis occurred in 6%. The mean survival time from diagnosis was 1199 days, (range 55 - >178 days) which suggests a less aggressive behavior for these tumors (J Comp Path 2007 136(4):231-9).

Histologic grade remains the most prognostic aspect associated with outcome; the high-grade tumors are more likely to be metastatic and have shorter overall survival times. In the classic Patnaik study of cases treated at the Animal Medical Center, 93% of patients with surgically excised Grade I tumors survived 1500 days (approximately 4 years), while 47% of Grade II and 6% of Grade III tumors treated with surgery alone survived for this period of time. Overall, around 50% of all patients in this study were cured by surgery. Proliferative indices (Ki67, AgNor scores) as well as evidence of abnormal c-Kit staining patterns or c-Kit oncogene mutations are associated with a worse outcome (BMC Vet Res 2008 4:32; Vet Path 2007 44(3): 298-308). Recently, mitotic index (MI) has been found to predict outcome very well, when, of 57 tumors evaluated, dogs having 1-7 mitotic figures per 10 high power fields (400x) had a median survival time of 18 months, vs. dogs with >7 mitotic figures per 10 high power fields having a survival time of 3 months. Dogs with a MI of <1 did not reach a median survival during the course of the study. (Vet Path 2009, epub ahead of print). In another study, for Grade II MCT with a MI ≤5, the median survival tie was 70 months, vs >5 with a median survival time of 50 months. However, for Grade III lesions with a MI ≤5 the median survival time was not reached, while for Grade III lesions with a MI of >5, the MST was <2 months. (Vet Path 2007, 44(3):335-41). Thus, apart from all other prognostic proliferative and kit mutation variables, the mitotic thoracic radiographs, abdominal ultrasound, liver and splenic fine needle aspirates, bone marrow aspiration, and buffy coat analysis. However, in February of 2000, the Veterinary Cancer Society hosted a focus meeting about canine mast cell disease. At this meeting, changes in staging protocols were recommended. These recommendations were based on the observation that buffy coat blood tests for mast cell leukemia, ultrasound evaluation for liver and spleen involvement, and bone marrow analysis yielded less that 2% positive results in a large series of more than 100 cases. These recommendations have not been uniformly accepted throughout the veterinary oncology community, however. More recently, a 5 year retrospective ultrasound study from Tufts revealed that in 19 patients, mast cell tumors may be detected in the abdominal cavity as organomegaly, diffuse hyperechoic lesions, focal hypoechoic lesions, or the liver and spleen may be completely unremarkable sonographically and yet still yield mast cell disease on cytology. Feline mast cell disease might be detected as thickening at the ileoceccolic junction or loss of intestinal wall layering. Mast cell tumors that are destined to become metastatic are generally the Grade III tumors.

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This index is very critical to counseling clients on the need for additional therapy.

**Treatment** - Therapy for mast cell disease is varied depending upon the histologic grade of disease, the clinical stage, and the availability of modalities such as radiation therapy. For the most part, surgery is still the mainstay of therapy for local mast cell disease. Surgery with 3 cm margins into normal tissue has been traditionally recommended and is often curative for lower grade lesions. Recently, researchers have questioned the need for such extensive margins, particularly in Grade I disease. A study from the Animal Medical Center of 21 cutaneous MCT patients suggested that 2 cm lateral margins and a deep margin of 1 fascial plane is sufficient to clear the local disease. The definition of what constitutes a “dirty margin” on histology is also subject to debate. Because mast cells normally reside in dermal tissues, it is possible that the pathologist may report normal mast cells at the margin of excised tissue. In fact, in one study only 30% of cutaneous mast cell tumors with histologically declared incomplete margins ultimately recurred, suggesting that normal resident mast cells are misread as neoplastic in 70% of these cases. Unfortunately, there is no simple marker that can differentiate malignant from benign resident mast cells. Thus, more conservative surgical excision is recommended by some authorities. However, in 30% of cases, due to the size and/or location of the lesion, surgery may be truly incomplete. In these cases, wider surgical margins may be obtained, or radiation therapy for microscopic disease in the tumor bed may be recommended.

**Radiation therapy** for incomplete margins or for non-resectable disease has a high probability of success in controlling local MCT. In one study of 95 MCT's treated on 85 dogs, 79% were free of tumor at one year and 77% were tumor free at 2 years. Another recent study of dogs that were radiated for incomplete surgical margins showed 96% tumor free survival at 1 year and 88% tumor free survival from 2-5 years after radiation. Palliative radiation of Grade III MCT resulted in complete remission with a median duration of 33 weeks or a partial remission with a median duration of 16 weeks (all subject to improvement in quality of life).

**Chemotherapy** may be reserved for dogs with nonresectable or metastatic lesions. The efficacy of chemotherapy in preventing recurrence or metastasis of mast cell tumor has not been documented. Glucocorticoids are most commonly used in treatment of this disease. Intrallesional triamcinolone (1 mg/cm of tumor) may also be helpful, even in the setting of preoperative tumor reduction. L-asparaginase has been shown experimentally to be helpful in treating mast cell disease in dogs. Anecdotal reports of response to a variety of other chemotherapy agents exist. Agents that have shown efficacy include vincristine, vinblastine, cyclophosphamide, and doxorubicin. The nitrosourea agent CCNU (Lomustine) has been reported to induce responses in dogs with metastatic mast cell disease. However, the response to any of these agents is unpredictable and typically short lived in disseminated canine mast cell disease.

**Protocols for Mast Cell Disease:**

**Chlorambucil** (Leukeran®) 6 mg/ M² PO every other day, alternating with Prednisone 20 mg/ M² PO daily, then tapering to every other day. This protocol was recently reported to be associated with 533 day progression free survival
In 8/21 treated dogs, suggesting this inexpensive and non-toxic protocol may be helpful for some cases.

**Vinblastine** 2-3.0 mg/M2 IV every 2-3 weeks coupled with 2 mg/kg oral prednisone is reported to have a 47% response rate, although this study was retrospective and mixed dogs with surgically incomplete margins with those that had measurable disease. Still, the fact that a response rate was seen at all is of some interest, indicating that vinblastine does in fact have some efficacy in this disease. Recent studies of dose escalation of vinblastine to a maximum tolerated dose of 3.5 mg/m2. The lower dose of 2.0 mg/m2 was associated with 3 partial response of 77 day median duration, while the higher dose induced 1 complete and 6 partial responses of 63 days for the CR and a median of 28 days for the partial response. The 3.5 mg/m2 dose induced hematologic toxicity in approximately half the cases, and 2 dogs had sepsis (JVIM 2008 22(6):1390 – 6.) In another study of high dose vinblastine, 3/16 dogs had severe toxicity and one died.

**Modified CVP Protocol:** Cytoxan 200 – 300 mg/M2 divided over 4 consecutive days (Days 6, 7, 8, and 9). Vinblastine 2 –3 mg/M2 Day 1, Prednisone 20 mg/M2 PO EOD. This was reported by Robin Elmslie to result in a median survival of 18 months for high grade or metastatic MCT after surgical resection, and 5 months median survival for unresectable lesions.

**CCNU single agent therapy:** 50 – 70 mg/M2 PO q 21 days. Response rates have been reported to be 44% for bulky MCT lesions with this protocol.

**Molecularly Targeted Therapy** with a small molecular inhibitor of receptor tyrosine kinase signaling, which acts as a c-KIT inhibitor, has been carried out in the dog (Palladia, Pfizer), and those dogs with a receptor mutation were the ones most likely to respond. The registration trial for this compound evaluated the drug in 86 dogs in a blinded, randomized placebo controlled setting. 37.2% of dogs had complete response, and 25% had partial response vs 7.9% of 63 placebo control dogs. Of 58 dogs that received Palladia after placebo failure, 8 had complete and 16 had partial responses for a response rate of 41%. The overall response rate for all dogs on Palladia was 42.8% (21 CR, 41 PR) and the median duration of objective response was 12 weeks and time to progression was 18 weeks. Adverse effects were considered tolerable. (Clin Cancer Res 2009 15(11):3856-65). However, this product is now commercially available by limited license to oncologists and internists, and has the potential for significant adverse effects. Adverse effects seen with this product have been largely gastrointestinal signs, which are managed by supportive care and increasing the interval between doses to every other or every third day. Beginning the dose at 2.5 mg/kg every other day rather than the recommended 3.25 mg/kg, plus premedication with omeprazole, diphenhydramine, and low dose prednisone is reported to decrease adverse effects. However, dogs with significant gastrointestinal signs are at risk for ulceration and intestinal or gastric perforation, so drug should be discontinued in the case of GI signs, and possibly restarted after a “chemotherapy holiday” at a lower dose or increased intertreatment interval (Monday, Wednesday, Friday dosing).

Other receptor tyrosine kinase inhibitors have been evaluated in the dog, including a compound called masitinib, which resulted in improvements in survival and response rates. In 202 dogs with nonmetastatic, recurrent or nonresectable grade II or III MCT, dogs were
randomized to masitinib 12.5 mg/kg/day PO or a placebo. Time to tumor progression was 118 days for the active drug vs. 75 days for the placebo. In all dogs, but in previously untreated dogs median time to progression was 253 days for treated vs. 75 days for placebo treated dogs. These findings were seen whether dogs were affected by wild type or mutated c-kit, and those dogs that had stable disease or tumor response at 6 months follow up were highly likely to maintain stable disease for 2 years.

Imatinib mesylate (Gleevec) has been reported to benefit dogs whether or not the tandem duplication mutation in the activation domain of c-kit is present. Gleevec is administered at 10 mg/kg SID PO, and extreme care must be taken to monitor for evidence of what may be a lethal idiosyncratic hepatobiliary necrosis. Owners who elect to pursue imatinib therapy for their dog should be counseled that lethal toxicities have been seen, as well as complete clinical responses in dogs that have the activating c-kit mutation. In a recent Japanese study, 21 dogs with measurable MCT showed response within 14 days in 10/21 cases, and those dogs with kit mutation in exon 11 had a 100% response rate (JVIM 2008 22(4):985-8).

**Feline Mast Cell Tumors**

MCT occurs in the skin and in visceral sites in the cat. Skin tumor occurs in older (mean age 9 years) cats, with no observed sex predilection. Siamese cats are three times more likely than other breeds to develop cutaneous MCT, which are histiocytic in appearance and prone to spontaneous regression. Visceral MCT tumors occur in the spleen, mediastinum and nodes. There is no FeLV association. Cats also are prone to an aggressive intestinal form of MCT that is associated with vomiting, weight loss, diarrhea and anorexia. Tumors in the intestine are composed of poorly differentiated cells.

Most cutaneous MCT of cats are well differentiated and benign, but occasionally have been reported to metastasize and often appear as multiple lesions in the skin. Visceral MCT of the spleen may cause massive splenomegaly and vomiting due to GI ulceration from histamine release. When visceral organs such as spleen and liver are involved, mastocytethemia and bone marrow involvement may be detected on staging evaluation. Occasionally cats with visceral MCT will develop multiple metastatic foci in the skin. Mediastinal involvement presents like thymic lymphosarcoma, with dyspnea and pleural effusion. Cytology of the pleural fluid reveals mast cells and eosinophils.

**Staging** - Staging for MCT in cats involves a minimum database anduffy coat evaluation for occult mastocytethemia, thoracic radiographs and abdominal ultrasound with fine needle aspiration of involved organs, and possibly bone marrow aspiration.

**Grading** - The histologic grading system, as applied to canine MCT has been
shown in repeated studies not to be predictive of tumor behavior or of clinical outcome. Mitotic rate within feline tumors may be correlated with biologic behavior.

**Treatment** - Treatment of dermal MCT is surgery, which occasionally must be multiple due to the tendency of cats to have multiple solitary tumors over long periods of time. Because these tumors are well differentiated in general, surgery is curative most often for solitary lesions. Corticosteroids (1 mg/kg/day prednisone) may be helpful. Radiation therapy can be useful for nonresectable or invasive tumors. Visceral MCT in cats is variable in behavior. Cats may present with massive splenomegaly, prompting the clinician to render a poor prognosis. However, splenectomy alone results in median survival times of 12 months, with some cats reported to live 3 years or more. Treatment of gastric and duodenal ulcers is symptomatic as described in canine MCT. Intestinal MCT carries the poorest prognosis of all of these presentations. Intestinal MCT often is associated with systemic involvement and patients are debilitated from malassimilation before diagnosis. If possible, bowel resection with 5-10 cm margins should be performed. Corticosteroids may be palliative for these cats, but most with intestinal involvement die within 4 months of diagnosis. Recently, the use of imatinib mesylate (Gleevec) has been shown to improve outcomes in visceral MCT feline cases, at a dose of 10 mg/kg PO SID. In some cases, cats develop GI signs necessitating treated on an every other or every third day basis for quality of life concerns.

Systemic chemotherapy has been attempted for cats with disseminated MCT. Agents such as used for the dogs may; be tried. However, no reports of prolonged survival as a result of chemotherapy have been published. We have recently been conducting a clinical trial of CCNU chemotherapy (10 mg capsule per cat Q 21 days) with some positive responses observed. We have seen some responses to CCNU at 10 mg/cat PO Q21 days.