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CANINE MAST CELL TUMORS: MARGINS, MARKERS & PROGNOSTIC FACTORS

General Information

Mast cell tumors (MCT's) are the most common tumor in the dog and the second most common tumor in the cat. MCT's are primarily a disease of older dogs and cats, however, extremely young dogs and cats have been reported to have MCT's. Canine breeds reported to be at increased risk for MCT's are boxers, Boston terriers, Labrador retrievers, terriers and beagles. The only feline breed that has been reported to be at increased risk for MCT's are Siamese. Most reports show no significant gender predilection for MCT's in dogs or cats. The etiology of MCT's is presently unknown. Many have suspected a viral etiology due to MCT transplantability to susceptible laboratory dogs (extremely young or immunocompromised) with tumor cells and cell-free extracts. Recent evidence shows that a significant percentage of dogs with higher-grade MCT's have genetic mutations in c-kit (stem cell factor receptor) which may be responsible for the genesis and/or progression of MCT's in dogs. Not all dogs with MCT's have c-kit mutations, suggesting that they are not the only mechanisms for the development and/or progression of MCT's.

Eighty-five to ninety percent of dogs and cats with MCT's have solitary lesions. It is important to note that not all dogs or cats with multiple MCT's have metastatic or systemic mastocytosis. Studies suggest that well-differentiated MCT's are slow-growing, usually < 3-4 cm in diameter, without ulceration of overlying skin, variably alopecic and commonly are present for more than 6 months. In contrast, poorly differentiated MCT's are rapidly growing, variably sized (but generally large), with ulceration of the underlying skin and inflammation/edema of surrounding tissues and lastly rarely are present for more than 2-3 months before presentation. Since most MCT's are of moderate-differentiation, signs may be somewhere between these two extremes.

History & Clinical Signs

The history and clinical signs of dogs and cats with MCT's can be extremely variable. Most do not show any clinical signs referable to their MCT, however, some may have signs referable to the release of heparin, histamine and/or other vasoactive amines. Mechanical manipulation or extreme changes in temperature can lead to degranulation of MCT's and subsequent erythema/wheal formation (Darier's sign) and gastrointestinal ulceration (anorexia, vomiting, melena, etc.).

Diagnosis & Staging

Fine needle aspiration and cytology (FNAC) is the mainstay for diagnosis of MCT prior to surgical removal. Mast cells of MCT's have a characteristic discrete cell cytological appearance with eccentrically placed nuclei and abundant red to purple (ie metachromatic) cytoplasmic granules. Occasional MCT's, predominately undifferentiated MCT's, do not have the classic metachromatic cytoplasmic granules and must be diagnosed via other means (histopathology, special stains, etc.).
Once a diagnosis is obtained, staging (looking for disease elsewhere) is routinely recommended, however, the completeness of staging is presently extremely controversial. After an FNAC diagnosis of MCT has been made, this author recommends routine staging diagnostics (full physical examination, bloodwork/urinalysis, FNAC of any local lymph nodes and abdominal ultrasound) but studies show ultrasound to be a low yield diagnostic test. Additional diagnostics such as thoracic radiography and bone marrow aspiration/cytology may be employed, especially in dogs with prior MCT's and/or a strong clinical suspicion for metastasis.

The use of buffy coat cytology and liver/spleen FNAC is presently controversial in the routine staging of dogs with MCT and this author does not routinely employ these diagnostics for staging of MCT's in dogs. Some oncologists have begun to either not routinely utilize bone marrow aspiration & cytology (BMAC) for MCT staging, or have begun to utilize results of CBC/plt to delineate whether or not to perform a BMAC. This is incredibly controversial and results of a recent publication concerning incidence and risk factors of bone marrow infiltration for canine MCT will be presented at the lecture.

Treatment

Once the diagnosis of MCT has been made with FNAC and/or incisional biopsy and staging has been completed showing no evidence of metastasis to other sites, surgical excision is the preferred choice of therapy. The standard recommendation for complete surgical removal of MCT's has been three centimeters lateral and 1 fascial

plane deep to the MCT. The derivation of this recommendation is unknown. This author still recommends continuing use of 3 cm lateral margins and one fascial plane deep margins whenever possible, but we published studies which show that 2 cm lateral and one fascial plane deep margins are sufficient for most grade II MCT. At present, the Seguin et al grade II MCT in dogs paper (2001) has the best information even though the followup time was relatively short (median of only 540 days). Those investigators found a 5% recurrence rate in the face of clean margins, an 11% second primary tumor development rate, and a 5% metastatic rate.

A new grading system from Kiupel et al at Michigan State utilizes a low vs high system and has been found to be more predictive of aggressive biologic activity than the previous Patnaik grade I/II/III system. Approximately 5-15% of dogs with an MSU "low" grade designation will go on to have aggressive biologic behavior, whereas those dogs with an MSU "high" grade designation and/or a mitotic index ("MI") will routinely have an aggressive course and require complete local tumor control as well as a high propensity for metastasis.

Recent studies in cats with skin/SQ MCT suggest that the vast majority are minimally invasive tumors with low recurrence rates suggesting that as wide and deep surgical margins may not be as necessary in cats as it is in dogs. It can not be over-emphasized as discussed above that cats with dermal MCT should be staged to ensure they do not have a splenic primary MCT that is metastasizing to dermal and/or other sites.
Dogs and cats with incomplete surgical removal of their MCT should undergo re-resection whenever possible. When re-resection is not feasible, external beam radiation therapy has been found to be an excellent post-operative therapeutic modality affording 75-85% control at 4-5 years in dogs with incompletely resected grade II MCT. Recurrence rates for completely resected grade II MCT hover in the 5% range in the veterinary oncology literature. Recurrence rates for incompletely resected MCT's hover in the 20-40% range across 6 studies. At present, we have to recommend additional local therapy for all incompletely resected MCT's in the face of such low-moderate recurrence rates, but additional recent studies suggest results from an MCT panel help better predict which cases truly need additional local therapy.

The results of a study utilizing radiation therapy for incompletely resected grade III MCT in dogs has been published by Hahn et al from Gulf Coast Veterinary Specialists. Thirty-one dogs received 52 Gy of external beam radiation in 18 fractions on a M-W-F basis to the surgical site and draining lymph nodes with no additional therapy (ie no chemotherapy). These investigators found a median survival time of ~ 28 months (range 3-52 months). Only one dog went on to develop systemic MCT metastasis. The results of this trial are highly controversial within the veterinary oncology community as previous metastatic rates for grade III MCT have been reported to be 55%-96%. At this time, most oncologists are continuing to use chemotherapy in the treatment of grade III and/or MSU "high" grade MCT's.

As discussed above, surgery should be considered the mainstay of therapy for MCT's. Chemotherapy is a very distant modality that may be useful for dogs and cats with systemic or metastatic mast cell tumor. Recent studies suggest that CCNU (lomustine), vinblastine, possibly cyclophosphamide and finally prednisone have limited activity against MCT. The results of studies utilizing chemotherapy and/or Palladia will be presented in detail at the lecture.

Prognosis
Histopathologic examination of MCT's has been found to be an important prognostic indicator by multiple groups. The Patnaik grading scheme (well-differentiated = grade I, moderately-differentiated = grade II and poorly-differentiated = grade III) has shown that 83%, 44% and 6% of dogs with grade I, II and III tumors were alive approximately 4 years after surgery, respectively. This grading scheme has not been found to be of use for cats with MCT. The aforementioned MSU low vs high grading system has shown 85-95% long term survival after appropriate local tumor control in dogs with MSU "low" grade tumors. Additional negative prognostic factors include advanced stage, caudal half of body location, high growth rates, aneuploidy and presence of systemic signs. Newly discovered molecularly-based negative prognostic factors include increased AgNOR (silver nucleolar organizing regions) scores, increased PCNA/Ki67 immunohistochemistry (IHC) expression (proliferation markers), increased vascularity and/or mitotic index and increased c-kit IHC expression. The use of MCT panels of the aforementioned prognostic factors is strongly recommended due to their significant

predictive ability for both the subsequent development of metastasis as well as subsequent development of recurrence, especially in those patients with clean but close or incomplete resections.

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