The Great Pretender:

Jennifer Black

Mississippi State College of Veterinary Medicine

Class of 2019

Clinicopathologic Conference

August 24, 2018

Advisor: Jesse Grady, DVM, MS

Introduction:

Mast cell tumors (MCTs) are among the most common skin tumors found in dogs and constitute approximately 20-25% of the skin and subcutaneous tumors seen by veterinarians.[1] Brachiocephalic breeds such as Boxers and Boston Terriers as well as Golden Retrievers are considered at a higher risk for MCTs.[1] MCTs can develop at any age but typically occur in middle aged to older dogs with the average age being 8.5-9.5 years with no apparent gender predilection.[2]

MCTs have been referred to as "The Great Pretenders" for their ability to "LOOK and FEEL" like anything. This includes a soft, subcutaneous, moveable mass that can easily be mistaken for a lipoma.[3] They can appear as a single cutaneous nodule but between 5-25% of canines are affected with multiple nodules that will either appear synchronously or sequentially.[4] They can be slow growing or acute, often "appearing overnight" to owners. Local signs can vary from non-painful swelling to intense pruritis, ulceration, erythema, bruising or prolonged hemorrhage.

Initial History and Presentation:

Zoey is a 13-year old Italian Greyhound who presented to the Mississippi State University College of Veterinary Medicine Community Veterinary Services on December 15, 2017. Zoey's owners first noticed signs of pain including trembling, guarding and keeping her head down 3 days prior to presentation. On closer inspection they observed "a large mass on the right side of her neck cranial to her scapula." They stated the mass appeared quickly, arising overnight. Given Zoey's small stature, short fur and how attentive her owners usually are this

scenario was deemed likely. Zoey's owners gave her ¼ tablet of Carprofen at home and stated that appeared to help. She also takes Benadryl 12mg (2.5mg/kg) twice daily.

Zoey has a history of having two mast cell tumors removed adjacent to the area of the current mass. On January 4, 2016 Zoey had a 6 x 6 x 1.5cm mass removed from in between her shoulder blades. The biopsy report revealed the mass to be a low grade mast cell tumor with wide surgical margins. On January 11, 2017 a second mast cell tumor (~1x1x1cm) was removed from the dorsal aspect of the right shoulder near the previous incision site. The biopsy result revealed a mast cell tumor within the dermis that was a low grade by the Kiupel scoring system and a grade II by the Patnaik scoring system. Surgical excision was complete with 12 mm lateral and 2mm deep margins including the underlying muscle layer.

Upon presentation Zoey was bright, alert and responsive. She was thin with a body condition score of 4/9. She weighed 4.5kg. While walking she walked with a hunched appearance with her abdomen tucked. She carried her head low. She had a large mass on the right side of her neck cranial to the right scapula and ventral to the scar from her previous mass removal. The mass measured approximately 4.5 x 3.6 x 2 cm. It is firm, slightly moveable and painful to the touch. No abnormalities were heard upon auscultation of the heart and lungs. All other parameters were within normal limits.

On December 13, 2017 a fine needle aspirate was performed. The submitted slides were of low cellularity with moderate blood contamination. There were low numbers of spindle to stellate cells that were mostly individualized. These cells had oval to elongated nuclei with a basophilic cytoplasm. The observed cells were of moderate atypia and a diagnosis of sarcoma was suggested however there was not an adequate number of cells to allow for a definitive

diagnosis. At this time Zoey was prescribed Galliprant 2mg/kg SID for pain and inflammation for 14 days, Gabapentin 11mg/kg BID for 7 days and Benadryl at 5.5mg/kg BID.

On December 15, 2017 Zoey returned and an incisional biopsy was performed. The biopsy showed subacute hemorrhage with early fibrosis. Multiple areas of hemorrhage were observed in which the red cells extend through and expand the pre-existing connective tissue. The hemorrhage appeared to be several days old with early fibroblast proliferation. Scattered small accumulations of neutrophils and occasional eosinophils were also observed. No evidence of neoplasia could be noted at that time. However, the cause of the hemorrhage was uncertain and underlying neoplasia could not be ruled out.

On December 19, 2017 (6 days after initial presentation) Zoey returned for chest radiographs. There was no evidence of nodular pulmonary metastatic neoplasia at that time. The mass was measured and had decreased in size to ~3.0 x 2.7 x 0.8 cm in size and did not appear painful.

In January and February of 2018, the mass had regressed and Zoey appeared to be doing well. On March 16, 2018 Zoey returned to have a mass checked on her right cranial shoulder. Her owners stated it had reappeared within the last two weeks and did not appear to be painful. It was bi-lobed, firm and measured 3 x 4 x 1 cm. All other aspects of her physical exam at that time were normal. A fine needle aspirate was taken from the mass on the right cranial shoulder. The sample slides contained high numbers of mostly well granulated mast cells. Zoey was diagnosed at this time with a mast cell tumor with fibroblast proliferation and macrophagic inflammation. At this time Zoey was placed on Prednisolone at 0.5mg/kg SID and Famotidine 1mg/kg BID.

On March 22, 2018 Zoey was seen by Internal Medicine Services for an oncology consultation and staging. The previously noted mass in the area of the right prescapular lymph node measured 2.1 x 2.6 cm. A CBC revealed a marked decrease in lymphocytes at 525/uL (1200-6500/uL). A Chemistry panel and measured clotting times revealed no clinically significant findings. Abdominal radiographs showed no clinically significant findings. During abdominal ultrasound FNA's were collected from the spleen, liver and left pre-scapular lymph node. No cytologic evidence of metastatic neoplasia were observed. A thoracic CT with contrast was performed. Findings included a large, irregularly marginated, soft tissue mass within the right lateral subcutaneous fat of the thoracic limb. It is deep to the right brachiocephalic muscle, adjacent to and encircling the right supraspinatus muscle and its tendon of insertion, and in the region of the right superficial cervical lymph node. This mass measures approximately 2 x 2.5 x 4 cm. The right superficial cervical lymph node was not identified. Inability to identify the cervical lymph node could be due to metastasis and effacement or prior surgical removal although it was not previously recorded as removed in the medical records. At this time it was recommended that Zoey have the mast cell tumor removed by MSU CVM surgery services.

Pathophysiology:

Mast cells originate in the bone marrow and play an important role in mediating the inflammatory response[2] and control of vascular tone[1]. They contain a large array of intracytoplasmic bioactive molecules including heparin, histamine, leukotrienes, and several cytokines.[1] Mast cells are found in most organs and tissues of the body but highest concentrations are found in locations that interface with the environment such as the skin, the lungs and the gastrointestinal tract.[4] Despite this most canine mast tumors occur in the dermis or subcutaneous tissues. Visceral mast cell tumors (disseminated or systemic mastocytosis) are

almost always preceded by an undifferentiated primary cutaneous tumor, and primary mast cell leukemia is extremely rare.[2,5] Cutaneous mast cell tumors have shown site predilection and are most common on the trunk (48-65%), followed by the extremities (25-47%) and the head and neck (10-13%).[5]

The etiology of MCTs is unknown but as with most neoplasms is probably multifactorial, and the well-documented breed dispositions likely indicate an underlying genetic component.[2] Recent work has implicated the stem cell factor receptor KIT, in the etiology of canine MCTs.[4,5] The majority of canine (and human) mast cell neoplasms express the tyrosine kinase growth factor receptor KIT, and a large minority of canine MCT (20-50%) possess a mutation in the c-kit gene coding for the KIT protein. The c-kit gene codes for a transmembrane protein that serves as the receptor for the growth factor stem cell factor, important in the maturation of normal mast cells and other hematopoietic cells. Mutations can allow the cells to proliferate and survive even in the absence of bound stem cell factor leading to unchecked growth.[2] So far no genetic defects in c-kit are identified in more than 60% of canine MCTs. This suggests that mutations in this gene are associated with the development or progression of some MCTs but mutations in other genes are likely involved in the initiation or progression of most canine MCTs.[4]

Some authors have suggested that chronic cutaneous inflammation may play a role in MCT development as MCTs have been found in sites of chronic inflammation or injury, such as burn scars. However, only rare cases of MCTs associated with chronic dermatitis, scar formation or the application of skin irritants have been documented.[4]

Diagnostic Approach and Considerations:

As mentioned previously MCTs have been referred to as the "Great Pretender" and can look and feel like anything. Because of this a MCT tumor should be considered as a differential for any skin nodule. Palpation of MCTs occasionally causes degranulation with release of histamine and other vasodilators that cause local vasodilation, edema and erythema, this is referred to as a Dariers sign[4] and is considered diagnostically significant. Systemic effects may also be observed due to a paraneoplastic syndrome. Increased concentrations of circulating histamine have been associated with GI ulceration and rarely arrhythmias, hypotension and shock[5].

The evaluation of a dog with a suspected MCT should include a fine needle aspirate (FNA) of the affected area.[1] FNA yields a correct diagnosis in 92-96% of histologically confirmed canine MCTs.[4] MCTs consist of a monomorphic population of round cells with prominent intracytoplasmic purple granules and eosinophils are frequently present in the smear.[1] Poorly differentiated mast cell tumors may lack the characteristic granules and a cytologist will suspect a higher grade MCT when cells are very pleomorphic.[6] Identification of MCT by cytology is important because it can help with surgical planning and treatment options. Most notably pre-medication with H1 and H2 receptor blockers and more extensive planning for appropriate surgical margins.[3]

After identifying the mass as a MCT you should proceed with staging based on the presence or absence of negative prognostic indicators. MCTs metastasize first to the regional lymph node and then to the spleen and liver. The minimum work-up should include a CBC, CHEM, UA, FNA of the draining lymph node (especially if enlarged) and abdominal radiographs and ultrasound. Thoracic radiographs are often not indicated unless the draining

lymph node is in the thorax because MCTs rarely metastasize to the lungs. There are 4 clinical stages for canine mast cell tumors.

1. One tumor confined to the dermis without regional lymph node involvement
2. One tumor confined to the dermis with regional lymph node involvement
3. Multiple dermal tumors or a large infiltrating tumor with or without regional lymph node involvement
4. Any tumor with distant metastases or recurrence with metastases[1]

Each category is further sub categorized as a. no systemic signs or b. with systemic signs.

After surgical excision the mass should always be submitted for histopathology for grading. Because neoplastic cells often extend beyond the observable or palpable tumor mass, completeness of excision can only be determined by means of histologic examination. After MCT excision, local recurrence occurs in 0-50% of dogs and distant recurrence or de novo development occurs in 11-38% of dogs.[8]

There are two accepted grading systems for cutaneous canine mast cell tumors. The Patnaik system which has 3 grading tiers.

1. Grade 1 -Well differentiated – benign, most develop slowly and persist for years
2. Grade II - Intermediate Differentiated – very unpredictable
3. Grade III - Poorly Differentiated – show aggressive growth and high recurrence potential.

Because most MCTs would fall in the grade II category and to help better predict behavior of mast cell tumors a second grading system based on two tiers, the Kiupel system, was introduced. According to this system high grade MCTs were significantly associated with shorter time to

metastasis or new tumor development, and with shorter survival times. The median survival time for high grade MCTs was less than 4 months but more than 2 years for low grade MCTs.[6]

Treatment and Management Options:

Surgery is the treatment of choice for primary cutaneous tumors located in areas amenable to excision.[7] Current recommendations are 3cm lateral margins and 1 fascial plane deep for grade III mast cell tumors and 2cm lateral margins and 1 fascial plane deep for grade 1 and II MCTs[6]. Because often the grade of the mast cell tumor is not known until after surgical excision, wider margins are taken when poor prognostic indicators are present. After resection of grade II MCT, local regrowth rates from 0 to up to 27% have been reported for both completely and incompletely excised tumors.[8] Weisse et. al performed a retroactive study in 2002 in which they found 89% of canines in their study with completely excised tumors had complete local control after 3 years.[9] However, it is also reported that after MCT excision, local recurrence occurs in 0-50% of dogs and distant recurrence or de novo development occurs in 11-38% of dogs.[8] When local recurrence or new MCTs form individual staging and grading is required.

For incompletely excised mast cell tumors a second surgery is recommended to obtain clean margins. If clean margins cannot be obtained or a second surgery cannot be performed, then radiation (RT) can be used as an adjunct therapy. Two-year control rates of 85 to 90% can be expected when incompletely excised low- or intermediate-grade MCT are treated with RT.[2]

In dogs with locoregional lymph node metastasis, a poor prognostic variable, adjunct chemotherapy and radiation have been recommended and implemented with increased survival and disease free intervals than dogs treated with surgery, or surgery and chemotherapy alone.[10] However, the need for adjunct chemotherapy in these cases is questionable.[4] MCTs appear to be

quite resistant to the effects of chemotherapy because many different agents have been used with little reported efficacy and most responses have been of short duration.[4]

Case Outcome:

On March 27, 2018 Zoey had the mast cell tumor in the region of her right pre-scapular lymph node removed. The vagosympathetic trunk was carefully dissected so it would not be inadvertently transected. The transected tumor was submitted for biopsy. It was a well demarcated subcutaneous mass composed of large numbers of neoplastic mast cell with deep margins at 1 cm and lateral margins in two sections were narrow at <0.5cm. It was deemed a low grade tumor due to its low mitotic rate, well demarcated nature and absence of multinucleated giant cells.

Because Zoey's first two mast cell tumors were located in similar locations (the dermis) and had similar characteristics on the histopathology reports it is believed that the 2nd mast cell tumor in January 2017 is a recurrence of the first. The third mast cell tumor was a little lower on the shoulder (pre-scapular area), located in the sub-cutaneous region and although categorized as low grade more mitotic figures were observed than in the previous tumors. After a consultation with oncology it is believed the third mast cell tumor is a separate occurrence from the first two.

Zoey's sutures were removed on April 13, 2018 and she appeared to be doing well. She visited MSU-CVM over the following months several times on unrelated matters. On August 19, 2018 (~5 months post-surgery), Zoey's owners contacted their primary veterinarian to tell him that she had developed another mass at the last excision site. They state they do not want to pursue surgery at this time. He is currently working with them to set up an appointment for a diagnostic work-up and to discuss potential treatment options.

References:

1. Couto, C Guillermo. Oncology. In: Nelson, Richard W. Couto, C Guillermo, eds. Small Animal Internal Medicine. 5th ed. St. Louis MO: Elsevier, 2014; 1191-1194

2. Rogers, Kenita S. Mast Cell Disease. In: Ettinger, Stephen J., Edward, Feldman. In: Textbook of Veterinary Internal Medicine Vol 2. 7th ed. St. Louis, MO: Elsevier Saunders, 2010; 2164-2176

3. Thamm, Douglass H. Demystifying canine and feline mast cell tumors. Southwest Veterinary Symposium. 2017.

4.Welle, MM. Bley, CR. Howard, J. et al. Canine mast cell tumors: a review of the pathogenesis, clinical features, pathology and treatment. Vet Dermatol. 2008;19(6):321□339.

5. Shaw T., Kudnig S. T., Firestone, S. M. Diagnostic accuracy of pre-treatment biopsy for grading cutaneous mast cell tumours in dogs. Vet Comp Oncol 2018;16: 214-219

6. Blackwood, L., Murphy, S., Buracco, P., et. al. European consensus document on mast cell tumours in dogs and cats. Vet Comp Oncol 2012;10;1-29

7. Scarpa, Filippo., Sabattini. Silvia., Marconato, Laura., et al. Use of histologic margin evaluation to predict recurrence of cutaneous malignant tumors in dogs and cats after surgical excision. JAVMA 2012; 240(10): 1181-1187

8. Fulcher, Ryan P., Ludwig, Lori L., Bergman, Philip J., et. al. Evaluation of a two-centimeter lateral margin for excision of grade I and grade II cutaneous mast cell tumors in dogs. JAVMA 2006;228(2):210-215

9. Weisse, Chick., Shofer, Frances S., Sorenmo, Karin. Recurrence Rates and Sites for Grade II Canine Cutaneous Mast Cell Tumors Following Complete Surgical Excision. J Am Anim Hosp Assoc 2002; 38: 71-73

10. Lejeune, A., Skorupski, K., Frazier, S. et. al. Aggressive local therapy combined with systemic chemotherapy provides long-term control in grade 11 state 2 canine mast cell tumour: 21 cases (1999-2012). Vet Comp Oncol 2013;13 (3) 267-289