The Pet Oncologist

Prognosis and Treatment Options for Canine Mast Cell Tumours

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Introduction

These notes will provide an overview of canine mast cell tumours – incidence, signalment, breed associations, clinical presentation, biologic behaviour and diagnosis. The main focus is on identifying and understanding the prognostic factors and treatment options available for canine mast cell tumours. Veterinarians that will benefit most from these notes are primary care veterinarians who wish to learn more about canine mast cell tumours, and how to diagnose, approach and manage canine mast cell tumours that are encountered in every day clinical practice.

Overview of canine mast cell tumours

Incidence & signalment

Mast cell tumours (MCTs) are one of the most common cutaneous tumours in dogs accounting for between 16-21% of all cutaneous tumours. MCTs typically affect older dogs (mean age of approximately 8-9 years); however, young dogs can also be affected. There is no apparent sex predilection. The breeds most at risk for MCTs include dogs of bulldog decent (boxer, pug, Boston terrier, English bulldog), Labrador and golden retriever, Staffordshire terrier, schnauzer, beagle, Chinese shar-pei and Weimaraner. However, most occur in mixed breed dogs.

Breed associations

Dogs of bulldog ancestry are at higher risk of MCT development but typically present with low-grade mast cell tumours. Boxers have a higher incidence of well-differentiated (i.e. low grade) MCTs. Pugs typically present with multiple low-grade mast cell tumours. Shar-peis typically present with biologically aggressive mast cell tumours.

Clinical presentation

MCTs generally present as solitary masses in the dermis and subcutaneous tissue in the trunk, perineum or limbs. However, approximately 10-15% of dogs present with multiple lesions and they can occur in any location. It is important to note that cutaneous MCTs have an extremely varied range of clinical appearances that they are sometimes inadvertently mistaken for nonneoplastic lesions or misdiagnosed clinically as a lipoma.

Some dogs present with no clinical signs of illness. While other dogs present with systemic signs of illness from the release of histamine, heparin, and other vasoactive amines from mast cell granules. Dogs with substantial MCT burden (i.e. large tumours, metastatic disease, systemic disease) are much more likely to present with clinical signs related to the release of mast cell mediators. These may include hyporexia, vomiting, diarrhoea, melaena, fever, peripheral oedema, and rarely collapse. Occasionally manipulation during the examination of MCTs results in degranulation and subsequent erythema and wheal formation referred to as 'Darier's sign'. It may also occur spontaneously, and owners may describe the tumour as periodically ‘waxing and

waning' in size. It is also important to be aware that MCTs can bleed excessively at the time of biopsy or surgery, due to the degranulation of heparin and other vasoactive amines.

MCTs typically spread first to the local lymph nodes, then to spleen and liver. Other visceral organs may be involved; however, lung involvement is rare.

Diagnosis

A diagnosis of MCT can be obtained by cytology which has an accuracy of 92-96%. MCTs usually exfoliate well and have characteristic 'metachromatic (purple reddish) intracytoplasmic granules which contain heparin, histamine, eosinophilic chemotactic factor, proteolytic enzymes and in cats, serotonin. Sometimes the intracytoplasmic granules will stain poorly with Diff-Quick but will stain after toluidine blue or Wright's (Giemsa) stain. A biopsy is sometimes recommended to grade the tumour before definitive surgery.

MCTs typically spread first to the locoregional lymph nodes. Therefore, staging involves fine-needle aspirate samples of the regional lymph nodes for cytology and/or biopsy, even if the lymph nodes are normal in size. Abdominal ultrasonogram is recommended for assessment of metastasis to intraabdominal lymph nodes or organs (particularly the spleen and liver). If there are any abnormal sonographic findings, fine-needle aspirates for cytology is recommended. For dogs with high-risk MCTs (i.e. Patnaik grade III, Kiupel high-grade, mitotic index >5, lymph node metastasis, recurrent mast cell tumour, recent rapid growth/ulceration and high-risk locations), fine-needle aspirates for cytology of both the spleen and liver are recommended even if they appear sonographically normal. Abdominal ultrasonogram alone is a poor predictor of metastasis to the liver in the spleen in dogs with high-risk MCTs. Three-view thoracic radiographs rarely demonstrate MCT metastasis; however, it is reasonable to perform them before an expensive or invasive procedure to rule out an occult cardiopulmonary disease that could complicate anaesthesia or unrelated disease processes (e.g. primary lung tumour). The incidence of bone marrow infiltration at the time of MCT diagnosis is approximately 3%. Therefore, this test is not routinely performed in staging canine MCTs. Haematology, serum biochemistry and urinalysis are recommended to assess the general health of the dog and determine if there are any co-morbidities.

Prognosis

The prognosis for canine MCTs is highly variable, sometimes unpredictable and depends on several factors. Unfavourable prognostic factors include MCTs that are Kiupel high grade, Patnaik grade III, high mitotic index (>5), *c-kit* mutation-positive, KIT (CD117) staining patterns II or III, unresectable, positive Ki-67 or AgNOR status, incomplete surgical excision, presence of metastasis, systemic signs of illness, large (> 2.5-cm diameter), high-risk locations (e.g. visceral, gastrointestinal, bone marrow, preputial, scrotal, vulva, subungual or oral locations), Shar-pei breed, rapidly growing, ulcerated and recurrent MCTs. It is essential to recognise that multiple cutaneous MCTs are not considered a negative prognostic factor. It can be a nuisance and costly to remove but provided they are all completely excised low-grade MCTs; the prognosis can be excellent. Therefore, each MCT should be treated individually.

Histologic grade (using both Patnaik and Kiupel grading system) is the most consistent and reliable prognostic factor for canine MCTs. It is essential to ask the pathologist to grade via both schemes. Patnaik grade I and Kiupel low-grade MCTs generally have an excellent prognosis with complete excision. These tumours have a high chance of cure with median survival times > four

years, <10% rate of metastasis and <5% risk of local tumour recurrence. Conversely, Patnaik grade III and Kiupel high-grade MCTs have a worse prognosis. Even with complete excision, these tumours have a high risk of metastasis of approximately 55-96%, median survival times of between 2 to 4 months, and approximately 36% risk of local tumour recurrence. For dogs with Patnaik grade II MCTs, it can be challenging to predict biologic behaviour. In general, the risk of metastasis is approximately 5-22%. However, they can behave like Kiupel low grade or Patnaik grade III MCTs with variable median survival times and recurrence rates reported. In those cases, other prognostic factors (such as mitotic index and c-kit mutation status) are required to predict biologic behaviour.

Mitotic index (MI) is also an important prognostic factor for canine MCTs and refers to the number of mitoses per 10 high power fields (400 X). As a general rule of thumb, MI ≥ 5 to 7 is considered poor. Dogs with MI of 0 have an excellent prognosis where median survival times were not reached in the studies performed. Dogs with MI < 5 to 7 had median survival times of approximately 2 to 5 years. Dogs with MI ≥ 5 to 7 have median survival times of approximately 2 to 5 months.

Approximately 20% to 40% canine MCTs will have *c-kit* mutations (mainly Patnaik grade II and III MCTs), which are correlated with increased risk of local recurrence, metastasis, and death from the disease. In some studies, *c-kit* mutation-positive MCTs may be more likely to respond to Palladia®, showing response rates of approximately 70% compared to 40% in *c-kit* mutation-negative MCTs.

There are three different KIT staining pattern expressions on all mast cells, including (I) membranous, (II) focal cytoplasmic and (III) diffuse cytoplasmic staining patterns. The KIT staining pattern is determined by KIT immunohistochemical staining on histologic specimens and is not the same as the *c-kit* mutation status test. As a general rule of thumb, cytoplasmic KIT staining patterns II or III are associated with shorter survival times than KIT staining pattern I. However, this test should not be assessed in isolation to determine the prognosis for canine MCTs, and I do not recommend performing this test if you have already performed a c-kit mutation test.

Unfortunately, the prognosis for dogs with unresectable and metastatic MCTs is poor with a median survival time of <3 months with supportive care and prednisolone. Dogs with lymph node metastasis have a variable prognosis. Low grade or grade 2 MCTs have a median survival time >1.5 years after locoregional control, and with adjuvant chemotherapy, the median survival time is between 2 and 5 years. Unfortunately, high grade or grade 3 MCTs have a worse prognosis. The median survival time is around eight months in dogs that obtain locoregional control, compared to 1.5 months in dogs that do not obtain locoregional control. Around 27-48% of dogs that have lymph node metastasis die due to their MCT.

Treatment options

For tumours localised to the skin in areas amenable to wide excision, surgery is the treatment of choice. For grade I and II MCTs, 2-cm lateral surgical margins and one fascial layer deep to the tumour are recommended. For smaller MCTs <5-cm in diameter, at least 1-cm lateral surgical margins and one fascial layer deep the tumour are recommended. Histologic margins are considered complete if >5-mm margins and one fascial plane deep. For grade III MCTs, 3-cm lateral surgical margins and one fascial layer deep the tumour is recommended.

Not all MCTs that are incompletely resected will recur (18-61%). This depends on the histologic grade of the MCT. However, for high-grade MCTs, even if the histologic margins are complete, one in three dogs will develop MCT recurrence. Radiation therapy is a localised form of treatment that can reduce the risk of recurrence to around 5-10%. Radiation therapy can also be used in dogs with gross disease with a response rate of around 50% for around 6-12 months.

For dogs with high grade or grade 3 MCTs that have been completely excised, chemotherapy is usually recommended after surgery to try to improve survival and to try to delay the onset of metastasis. With this approach, the median survival times exceed >1 year, compared to 2-5 months in dogs treated with surgery only. There are many chemotherapy options available. The most common chemotherapeutics used are vinblastine and lomustine (CCNU). Other treatment options include chlorambucil, Palladia® (toceranib phosphate), masitinib and hydroxyurea. Prednisolone is recommended concomitantly. Chemotherapy and Palladia® can also be used in the gross disease setting. The response rates are around 40-90% and median survival times around 3-12 months.

Palladia® is an oral tyrosine kinase inhibitor that is indicated for the treatment of MCTs that are *c-kit* mutation-positive, grade 3, high grade, unresectable, metastatic or no longer responsive to chemotherapy. Palladia® will be discussed further in the presentation entitled 'How to give Palladia® in pets with cancer'.

All dogs with gross or macroscopic MCT (e.g. unresectable MCT) or when systemic signs are present should receive prednisolone, antihistamines and gastroprotectants. Prednisolone can inhibit canine MCT proliferation and induce tumour cell apoptosis in vitro. They may also decrease peritumoral oedema and inflammation associated with MCTs and clinically make dogs feel better (and usually within 24-48 hours). The response rate is approximately 20% to 70% and, occasionally, dogs may achieve a complete remission with prednisolone. However, remission duration is often short-lived for approximately two to three months. I prefer the antihistamine loratadine to inhibit histamine release because it also has been shown to inhibit the spontaneous growth of neoplastic mast cells in-vitro. I also prefer the gastroprotectant omeprazole to prevent histamine irritation to the gastrointestinal tract and for treatment of subclinical gastrointestinal ulceration, because it has the most robust clinical evidence for increasing the pH in dogs with gastrointestinal ulceration.

Vets, I hope this information helps you understand a bit more about canine mast cell tumours. If you have a question about canine mast cell tumours or have a dog that you would like evaluated, please do not hesitate to get in touch. Email: info@thepetoncologist.com.