



Mast Cell Tumors

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Mast cell tumor (MCT), also called mastocytoma, is a common skin tumor in dogs. The mast cell tumor is the most frequently diagnosed malignant skin cancer in dogs. Dogs are diagnosed at an average of 8 years old, although puppies as young as 4 months may be affected. Dogs can have multiple tumors, either concurrently or in sequence over time. Most mast cell tumors are easily removed without any further problems, while others can lead to life threatening disease. When the entire body is affected, the disease is referred to as mastocytosis.

Normal mast cells are present in most tissues, especially the skin, lungs and digestive tract. They are part of the immune system and function during inflammation and allergic reactions. Mast cells contain granules with large amounts of histamine, heparin, and proteolytic enzymes (enzymes which break down protein). These molecules are toxic to foreign invaders such as parasites, and when mast cells break apart (degranulate), the molecules are released. Although the chemicals are vital to normal immune function, they can be very damaging to the body in high concentrations.

A mast cell tumor is formed when a normal mast cell mutates and divides, creating a large group of many mast cells. When this happens, the cells of the tumor are unstable and may release chemical granules with simple contact, or even at random. The most significant danger from mast cell tumors arises from the secondary damage caused by the release of these chemicals, including ulcers within the digestive tract, hives, swelling, itching and bleeding disorders. Sites where the tumors are removed sometimes fail to heal and can become difficult to manage.

The behavior of mast cell tumors ranges from a single isolated skin mass to highly aggressive with invasion of local tissue and spread to distant organs. Microscopic examination of a mast cell tumor is usually the best predictor of the tumor's behavior and prognosis.

Symptoms

Mast cell tumors most commonly appear as a skin mass. The tumors can have a wide range in their appearance, including smooth pink lumps, ulcerated (raw) skin lesions and even soft tumors under the skin that may be misdiagnosed as a fatty lipoma. Mast cell tumors are known as "great imitators," and any lump or bump on a dog may be abnormal, may be cancerous and should be examined by a veterinarian.

One unusual characteristic of mast cell tumors is a tendency to change in size, even on a daily basis, due to the release of histamine and other chemicals. A tumor that randomly gets bigger and smaller may be a mast cell tumor.

The skin around a mast cell tumor may become inflamed and swollen, and additional raised skin nodules or hives may form nearby. Other symptoms of mast cell tumors can include:

- Enlarged lymph node
- Loss of appetite
- Abdominal pain
- Welts
- Collapse
- Vomiting

- Diarrhea
- Weight loss
- Bloody or black, tar-like feces

Causes

Mast cell tumors can develop in all ages and breeds of dogs. Certain breeds have a higher risk of developing mast cell tumors, including Boxers, Bulldog breeds, Bullmastiffs, Boston terriers, Golden retrievers, Labrador retrievers, Pugs, Rhodesian ridgebacks and Weimaraners, suggesting a genetic component.

c-Kit is a molecular receptor found on the surface of mast cells. Several studies have suggested the presence of mutations in the c-Kit receptor lead to malignant transformation of the mast cell.

Diagnosis

The most important diagnostic test is the microscopic examination of cells collected from the tumor, usually by fine-needle aspiration. This test will identify most mast cell tumors, including those underneath the skin that might be misdiagnosed as fatty tumor. A needle is inserted into the tumor, and cells are withdrawn to be placed on a microscope slide.

Some mast cell tumors must be diagnosed by biopsy or even special stains. Additionally, aspiration is not adequate for grading, which requires biopsy and histopathology.

General Health Assessment

The initial evaluation will include a detailed medical history and complete physical examination. A complete blood cell count, serum chemistry panel and urinalysis is performed to evaluate general health.

Local Lymph Node Aspiration

A fine needle aspirate from the lymph nodes nearest to the mass is also typically collected.

Other Diagnostic Testing

- If the tumor is located in an area easily accessible for surgery, and no obvious negative prognostic factors are present, the tumor is usually surgically removed and graded (see below). - If the tumor develops at a site where complete surgical removal is not possible and/or if additional negative prognostic factors are present, additional diagnostic tests should be considered prior to deciding a treatment plan.

Abdominal ultrasound (sonogram) is performed to examine the spleen, liver and abdominal lymph nodes. Ultrasound is highly useful for guiding collecting samples of these organs for microscopic examination.

Radiographs (x-ray studies) of the heart and lungs are not very helpful in determining the course of mast cell tumors, since this cancer rarely spreads to the lungs like many other forms of cancer. Radiographs are very useful to identify unrelated diseases that can complicate anesthesia and to examine lymph nodes in the chest cavity.

Bone marrow aspiration may also be recommended to evaluate for metastasis of mast cell cancer.

Buffy coat smear is a test for identifying large numbers of mast cells circulating in the bloodstream. While buffy coat smears were previously considered important for identifying mast cell metastasis in dogs, more recent studies have proven the test to be unreliable. This test is still recommended for cats with mast cell cancer.

Grading and Staging

Grading is the microscopic description of a tumor designed to predict the behavior of the cancer and its tendency to remain localized or spread throughout the body.

Staging refers to the extent that the cancer has invaded and spread (metastasized).

Tumor Grade

The tumor is examined microscopically by a pathologist and classified according to how it is expected to behave. Differentiation is the determination of how much a particular tumor cell looks like a normal cell; the more differentiated, the more like the normal cell. In general, the more differentiated the mast cell tumor is, the better the prognosis is.

- The Patnaik system uses three grades:

Grade 1 (I) is well-differentiated, and the tumor cells appear like normal mast cells.

Grade 2 (II) is moderately-differentiated, and the tumors may have minor abnormalities or invade into tissue layers deep to the skin.

Grade 3 (III) is poorly-differentiated, and may be difficult to confirm as a mast cell tumor without additional testing. These tumors carry the poorest prognosis but are fortunately the least common.

- More recently, the Kiupel 2-tier grading has become popular as a more simplistic and accurate method of categorizing mast cell tumors:

Low-grade: low numbers or absent mitotic figures and few nuclear changes

High-grade: mitotic index of 7 or higher, and/or frequently abnormalities in the nucleus of the mast cells

High-grade mast cell tumors have been associated with shorter time to metastasis or new tumor development, and with a shorter life expectancy of less than 4 months following surgery.

Grading helps to determine whether local treatment (most Grade 1-2/low-grade mast cell tumors) or treatment incorporating the entire body (Grade 3/high-grade mast cell tumors) is more appropriate.

Tumor Stage

Tumor stage refers to the extent to which the cancer has already metastasized (spread) at the time of diagnosis. Mast cell tumors most commonly metastasize to lymph nodes, liver and spleen, so much of the testing focuses on these areas. Tumors that are treated before they have invaded other tissues or spread to new locations have the best prognosis.

Staging is based on how many tumors are present, if the entire tumor was removed, and whether lymph nodes or other tissues are involved:

Stage 0: One tumor on the skin surface incompletely removed with no lymph node involvement

Stage 1: One tumor on the skin surface with no lymph node involvement

Stage 2: One tumor on the skin surface with lymph node involvement

Stage 3: Multiple skin tumors or infiltrating tumor(s) with or without lymph node involvement

Stage 4: Any tumor(s) with distant metastasis

This stage is subdivided into Substage A, in which there are no other signs, and Substage B, in which there are debilitating clinical signs such as vomiting and diarrhea.

Staging helps to determine whether local treatment (most mast cell tumors) or treatment incorporating the entire body is more appropriate.

c-Kit status

c-Kit is a molecular receptor found on the surface of mast cells. Several studies have suggested the presence of mutations in the c-Kit receptor lead to malignant transformation of the mast cell. Mutations of the c-kit receptor can be identified by special tissue analysis, and the presence of mutations is linked to more frequent mast cell tumor recurrence compared to tumors without mutations.

Treatment

Mast cell tumors are most commonly treated with surgery. Radiation therapy and chemotherapy may also be recommended, depending upon the malignant characteristics of the tumor. The goals of treating a mast cell tumor are to control the local disease and any other conditions associated with the tumor, and to prevent metastasis if at all possible.

Surgery

Aggressive surgical removal is the treatment of choice for a mast cell tumor. Mast cell tumors tend to be more locally invasive than their appearance suggests. Removal of a "safety margin" of approximately 1 inch of healthy appearing tissue surrounding the tumor should be included to ensure that the cancer is completely removed. The entire tissue sample is examined microscopically by a veterinary pathologist to determine whether enough normal tissue around the tumor was removed to be certain that all of the cancer cells were collected. If the margins are narrow or margins indicate there is still tumor left behind then a second surgery or even a course of radiation therapy may be desirable.

When a single mast cell tumor is present and the local lymph node contains metastatic cancer, removal of the positive lymph node significantly improves the prognosis when compared to treatment without removing the lymph node.

Radiation therapy

Radiation therapy is the use of high-energy radiation to treat cancer. The combination of surgery and radiation therapy is highly effective for mast cell tumors that are located where wide surgical excision is not possible. This treatment option has certain drawbacks, which include cost, the limited availability of treatment facilities, and the need to sedate the patient for each of several doses. However, radiation therapy is an excellent tool to permanently eliminate any microscopic traces of a low-grade mast cell tumor when surgery cannot achieve clean margins.

Chemotherapy

Chemotherapy is the use of medication(s) to treat cancer. Traditional chemotherapy medications prevent cells from dividing, which makes these drugs particularly effective against cancer cells. Chemotherapy has the benefit of treating cancer throughout the body as the drugs are carried through the blood stream. Therefore, chemotherapy should be considered for dogs with high grade (Grade 3) and/or Stage 2 or higher mast cell tumors, since these dogs have high risk or confirmed for metastasis. Chemotherapy is recommended for patients with multiple simultaneously-occurring mast cell tumors, high-grade mast cell tumors and patients with metastasis to lymph nodes or internal organs.

Chemotherapy may also be helpful for reducing the size of a mast cell tumor prior to attempting surgery, as well as lowering the risk of tumor recurrence following narrow or incomplete surgical removal.

Conventional chemotherapy drugs for mast cell tumors include Vinblastine, Lomustine (CCNU) and Leukeran (chlorambucil). These are all human chemotherapy medications that have been adapted to use "off-label" in dogs and cats.

- **Vinblastine** is an injectable chemotherapy medication. As a cell divides, microscopic protein rods called microtubules pull the two cell halves apart. These important structural proteins must be functional or cell division cannot occur. Vinblastine is a microtubule poison, resulting in the death of the dividing cell. It is a member of the vinca alkaloid class

of chemotherapy drugs, extracted from the *Vinca rosea* plant. Vinblastine must be given intravenously, directly into the bloodstream. It will decrease the number of neutrophils, white blood cells that prevent bacterial infections, and may disrupt the normal lining cells of the stomach and intestines. Symptoms can include nausea, vomiting, diarrhea and/or lethargy. Symptoms are usually self-limiting and short in duration.

- **Lomustine (CCNU)** is an oral chemotherapy medication. It is a member of the nitrosurea class of chemotherapy agents that act by binding and disrupting cellular DNA in such a way that the DNA double helix strand cannot replicate. In addition to essentially tying DNA up, Lomustine also alters proteins to prevent cells from building DNA and RNA strands. Cells that multiply rapidly (and thus replicate their DNA rapidly) are especially targeted by Lomustine. Lomustine will also decrease the number of white blood cells as well as platelets, the blood cells that prevent uncontrolled bleeding. Lomustine may affect the patient's liver, and blood tests are essential for monitoring the safe use of this medication.
- **Leukeran (Chlorambucil)** is another oral chemotherapy medication. It is an alkylating agent, and its activity stems from cross-linking with cellular DNA and directing apoptosis or natural cell death. Leukeran can reduce normal blood cell numbers to unsafe levels, resulting in increased risk for infection, anemia and uncontrolled bleeding. Blood cell counts must be repeated frequently to identify side effects from Leukeran.

Targeted chemotherapy medications are now available for dogs with mast cell tumors: Palladia by Pfizer Animal Health and Kinavet by AB Science.

- **Palladia** (toceranib) is a tyrosine kinase inhibitor and works in two ways: by killing tumor cells and by cutting off blood supply to the tumor. Palladia specifically blocks several molecular targets (c-KIT, vascular endothelial growth factor receptor-2 [VEGFR-2], and platelet-derived growth factor receptor [PDGFR-beta]) found on the surface of certain cells and known to play a role in cancer. Palladia was evaluated in a clinical trial including 153 dogs with mast cell tumors that returned after surgery. In this study, dogs received either Palladia or placebo (inactive substance serving as a control) for six weeks. The results showed that 32 of 86 dogs (37.2%) who received Palladia responded to treatment, with seven dogs achieving complete response and 25 dogs achieving partial response. The time that passed before that cancer advanced in each patient was longer for dogs treated with Palladia compared to those treated with placebo. Dogs who had tumors with c-Kit mutations were more likely to respond to Palladia compared to dogs with no c-Kit mutation. Among the 62 dogs who responded to therapy, their response averaged 12 weeks and the time to tumor progression was 18 weeks. Side effects that occurred more frequently in dogs receiving Palladia (compared to placebo) included diarrhea, bloody stool, weight loss, lameness and low white blood cell numbers.
- **Kinavet** (masitinib) has been available in Europe under the name Masivet. It also specifically inhibits several molecular targets (c-Kit, PDGFR alpha and beta, and Lyn) found on the surface of certain cells and known to play a role in cancer. Masitinib was evaluated in a clinical trial with 202 dogs with mast cell tumors were randomized to receive either Masitinib or placebo. The time required for tumor progression for Masitinib was close to 6 months, compared to 2.5 months for dogs treated with placebo. For dogs who had tumors with c-Kit mutations, the time to tumor progression while receiving Masitinib was 7.5 months. The most common side effects of Masitinib are diarrhea and vomiting, and Masitinib cannot be used in dogs with certain liver and kidney conditions, anemia (low red blood cell count) or a low white blood cell count).

Prednisone

Prednisone is particularly helpful for treating mast cell tumors, both alone and in combination with other medications. Corticosteroids such as Prednisone are highly effective at protecting the body from histamine, heparin, and proteolytic enzymes that are released when mast cells degranulate. Prednisone may also be directly toxic to mast cells and may even result in a temporary remission of a mast cell tumor. Prednisone is particularly helpful for reducing the size of a mast cell tumor prior to attempting removal. Prednisone is inexpensive, readily available and relatively safe. Side

effects include increased drinking, urination, and appetite. More long-term effects include muscle loss, decreased immune function, enlargement of the liver and weight gain. Corticosteroids such as Prednisone are inexpensive medications and worth considering if other treatments are not available.

Other Therapy

In addition to treatment of the actual mast cell tumor, some patients may also require treatment with anti-histamine medications. The release of large amounts of histamine from mast cell tumors into the body can cause local inflammation and swelling around a mast cell tumor and significantly affect heart rate, blood pressure and other body functions. These effects may be reduced or prevented with the use of histamine-blocking medications. Such medications include H1 blockers (antihistamines such as diphenhydramine, hydroxyzine and others) as well as H2 blockers (antacids such as famotidine and others).

Severe digestive tract symptoms including vomiting, diarrhea and abdominal cramping from stomach ulcers are often the terminal effects of mast cell cancer, marking the end of quality of life. Therefore, controlling symptoms of histamine release may be more important than battling the cancer.

Outcome

Mast cell tumors generally respond well to treatment. The prognosis for dogs with mast cell tumors is dependent on a variety of different factors such as the tumor size, location, grade or symptoms. Tumor grade appears to be the most consistent prognostic factor for dogs with mast cell tumors. Well-differentiated mast cell tumors in the skin often can be treated successfully by aggressive surgery. High grade tumors are associated with aggressive tumor behavior, and most dogs die within 4 to 6 months after surgery as a result of metastasis and tumor degranulation. The addition of radiation therapy or chemotherapy can significantly improve the outcome for dogs at high risk for local tumor recurrence or metastasis, respectively.

Anatomic Location

Mast cell tumors arising in the nail bed, muzzle, and oral cavity often behave more aggressively. Dogs diagnosed with mast cell tumors in their internal organs (visceral mast cell tumor) face poorer prognosis compared to those in the skin. Previously it was thought that inguinal (groin) and perineal sites were associated with a poorer prognosis, but recent studies indicate this may not be true.

Dogs that develop one mast cell tumor may have a tendency to develop others during their lifetime. Owners of dogs that have been diagnosed with mast cell tumors must be vigilant in the future and should regularly inspect the skin on their dog's entire body for any signs of new tumors. This should be done for the rest of the dog's life. Even if no follow-up treatment is recommended, your pet should be evaluated on a regular basis for recurrence or spread of the mast cell tumor. Follow-up examinations are recommended every 2 to 3 months for the first year and then every 6 months ongoing for dogs with mast cell cancer.

Prevention

There is currently no known prevention for mast cell tumors. Because nearly half of dogs diagnosed with a mast cell tumor will develop more than one during their lifetime, affected animals should be monitored closely for any new skin lesions. New skin lumps and bumps should be examined by a veterinarian to be identified and treated as quickly as possible.

Not all veterinarians are comfortable treating mast cell tumors. Discuss with your veterinarian whether referral to a specialist would be best for you and your pet.

Please note that this information does not replace a direct consultation, with the patient and all clinical data, with a board-certified veterinary oncologist. To schedule an appointment with Dr. Sue Downing at Animal Specialty & Emergency Center, please call (310)473-5906, option 4.

Other Resources:

Read more about mast cell tumors and Palladia (toceranib) at https://www.mypalladia.com/PDF/Palladia_ClientInformationSheet.pdf

For additional information about Kinavet and mast cell tumors, go to <http://www.masivet.com/>

Veterinary Cancer Society has a [searchable clinical trials database](#) that you may access to see if there is a trial that may be of benefit for your pet.

