Mast Cell Disease

Mast cell tumors are a cancer of the mast cells. Mast cells normally reside in many tissues in the body, especially the skin, lungs, mouth, nose, conjunctiva of the eyes, and digestive tract. Mast cells are characterized by their intensely purple staining granules in the cells when examined under a microscope. Mast cells are part of the body’s immune system. They play an important role in allergies and defense against worm infestations.

Pugs seem to be one of the dog breeds that are especially susceptible to mast cell cancer, especially in the skin. About 20% of skin cancers are mast cell tumors. Once a pug has had one mast cell cancer, there is about a 15% chance that the pug will develop multiple mast cell tumors over his/her lifetime. Generally the tumors occur in middle aged or older pugs, but mast cell cancer can occur in young pugs as well.

When you find a lump or swelling on or in your pug’s skin, there is no one characteristic finding which will tell you if the lump is a mast cell cancer or a benign tumor. Sometimes the lumps are pigmented or bleeding. Sometimes they are rapidly change in size from day to day. The only way to make the diagnosis is by simple aspiration biopsy of the lump.

Once the diagnosis of mast cell tumors has been made, the cancer is are divided into four stages depending on how far the cancer has spread or if there are multiple tumors:

- Stage I - solitary tumor confined to the dermis (skin) without lymph node involvement.
- Stage II - solitary tumor with regional lymph node involvement.
- Stage III - multiple dermal tumors with or without lymph node involvement.
- Stage IV - any tumor with distant metastasis or recurrence with metastasis

Prednisone therapy (dosed at 1mg per kg per day) is recommended before surgical excision of mast cell cancers. Apparently about 70% of dogs will respond with a reduction in the size and volume of the tumor. (J Am Vet Med Assoc. 2008 Jan 1;232(1):53-62.) This makes excision of the tumor easier.

Surgical excision is the treatment of choice for Stage I tumors. There is not further treatment needed. New tumors may come up, and you have to keep an eye out for them by examining the skin of your pug regularly. All surgical excisions should have a wide margin (about 1.5 cm) of disease free skin taken at the time of the surgery.

What is done for Stage 2, 3, and 4 is the matter of some debate. If the tumor is on an arm or a leg, then that limb might be amputated and/or radiation therapy given to the area. Radiation is use to try to “sterilize” the area of stray cancer cells. My pugs never seem to get tumors in areas that are easily treated. Suppressive treatment with prednisone has been recommended in the past but prednisone seems to have no benefit in improving long term survival. More about treatment will be discussed below.
One of the important factors in determining treatment and survival with mast cell cancer is a determination of how nearly normal the mast cells from the tumor look when examined under a microscope. This is called the histiologic grade. Mast cell tumors are graded using a system developed by Patnaik as to the grade of the tumor (Vet Pathol. 1984 Sep;21(5):469-74. Expert Rev Mol Diagn. 2009 Jul;9(5):481-92.).

- Grade I - well differentiated and mature cells with a low potential for metastasis.
- Grade II - intermediately differentiated cells with potential for local invasion and moderate metastatic behavior
- Grade III - undifferentiated, immature cells with a high potential for metastasis

Grade I tumors are benign. Grade II tumors, which seem to be the most common in my experience, can behave either benignly or can be more aggressive. There is considerable variation in their biological activity. That is some tumors rarely spread or recur while other Grade II tumors tend to spread and recur. Grade III tumors are very malignant. Unfortunately there is not always a lot of agreement among pathologists as to the grade of a tumor.

Because of the variable behavior of mast cells graded as II, a number of other tests have been developed to try to sort out which tumors will be more aggressively. For example, one test is a silver (argyrophilic stain of nucleolar organizer regions or AgNOR score) stain of the mast cells. The black dots in the nucleolar region of the cell are counted. This information can be helpful in predicting survival. The higher the AgNOR score generally the poorer the prognosis because there is a greater likelihood that the mast cell cancer has or will spread. Another marker studied by immunohistochemistry is the marker Ki-67. Again, the higher the Ki-67 count, the poorer the chances are for survival. (Vet Pathol. 2007; May 44(3): 298-308.) Other markers are being studied and used, such as c-KIT since it has been observed that mast cell tumors with c-KIT mutations are associated with recurrent disease and death.

Before determining further treatment for the mast cell cancer, the veterinarian will have to do a careful physical examination palpating for enlarged lymph nodes. Splenic and other biopsies may need to be done to see if the cancer has spread to the spleen or bone marrow. Lymph nodes may need to be biopsied. All these are done with needle aspirations and not open surgery, but they do require anesthesia. Sometimes the search for splenic or liver involvement can be done with ultrasound which is then followed by biopsy. (J Vet Intern Med. 2009 Sep-Oct;23(5):1051-7. Epub 2009 Jul 28.) Pugs who have mast cell tumor in their liver and spleen live for a much shorter period of time than dogs who do not have tumor in their liver and spleen. Buffy coat smears used to be recommended to look for the presence of mast cell in the peripheral blood. This test is a waste of money. Most dogs with mast cells in their blood have worms or parasites and not mast cell disease.

Adjunctive therapy is usually given when there is evidence that the mast cell tumor has spread or if it has a higher histiologic grade. Therapies that are considered more traditional chemotherapy which have been studied include the following:

3. CCNU (or Lomustine) and vinblastine (Vet Comp Oncol. 2009 Sep;7(3):196-206.)
4. CCNU (or Lomustine) and prednisone (J Am Anim Hosp Assoc. 2009 Jan-Feb;45(1):14-8)
5. Vinblastine, cyclophosphamide, prednisone (Vet Comp Oncol. 2007 Sep;5(3):156-67.)

All these therapies have some toxicity and adverse events. All seem to improve survival when compared with dogs who received no adjuvant therapy. There is not enough current information to tell if any of these regimens is superior.

In addition to “traditional” chemotherapy, more targeted therapy for mast cell cancer has been developed. These new drugs bind to receptors on the cancer cell and on the blood vessels which feed the tumor. So both the cancer and the blood supply that feeds to cancer is killed. One, toceranib or Palladia, received FDA approval in June 2009 for use in treatment of mast cell cancer in dogs. This is a receptor tyrosine kinase inhibitor and should theoretically be superior to other chemotherapy agents. In the one published trial, about 40% of dogs responded to tocernib. (Clin Cancer Res. 2009 Jun 1;15(11):3856-65. Epub 2009 May 26.) Of those that responded, one-third had a complete response and two-thirds had a partial response. The drug is administered on an every other day or a Monday, Wednesday, Friday schedule. The side effects include loss of appetite, vomiting, diarrhea and bleeding from the digestive tract.

In addition to toceranib, another tyrosine kinase inhibitor has been shown to be effective in the treatment of mast cell disease, masitinib (Masivet) (J Vet Intern Med. 2008 Nov-Dec;22(6):1301-9. Epub 2008 Sep 24). Masitinib has not received FDA approval as of December 2009. [Masitinib is also used in humans and is being studies for the treatment of refractory rheumatoid arthritis. It is also being studied for use in other inflammatory diseases and cancer.]

I give my pugs who are diagnosed with mast cell disease diphenhydramine 25 mg and famotidine 5 mg every day twice a day to counter the histamine released from the mast cells. And I continue this for life though there is no published research evidence that this is effective.

Before any biopsy of masses that may contain mast cells, I would recommend talking with you veterinarian about pre-medicating your pug with diphenhydramine (Benadryl) 25 mg and famotidine (Pepcid) 5 mg (or cimetidine, Tagamet) because histamine can be released just from the biopsy procedure. I usually give the medication at home about 30 minutes before the procedure is done.

Cimetidine which blocks histamine 2 or H2 receptors is used primarily for treatment of acid reflux (heartburn) and gastric ulcers since it inhibits stomach acid secretion. It has also been noted to have some anti-tumor properties which included inhibiting metastasis of some cancer cells and well as the growth of cancer cells. (Int J Oncol. 2006 May;28(5):1021-30.) For a pug, the dose would typically be a 50-100 mg three times a day (usually dosed at 5-10 mg/kg). It is not known if other histamine 2 receptor blockers have a similar anti-tumor activity. Remember no over the counter medication such as cimetidine or famotidine should be given without prior
consultation with your veterinarian or veterinary oncologist.