Mast Cell Cancer

MAST CELL CANCER seems to be a particularly aggressive and troublesome problem in the Shar-Pei breed. The following discussion hopefully will provide you with some useful information.

1. **CAUSE:** Mast cells are a normal component of the body. These cells contain granules in their cytoplasm which contain heparin (an anticoagulant), serotonin (an inflammatory mediator), histamine, bradykinins, TNF-α and a number of other substances. The release of these vasodilator, nociceptive and proinflammatory molecules cause inflammation, itching, edema, vasodilation and attract other cells such as macrophages and white blood cells to the area. This response is usually helpful in responding to allergic reactions, foreign objects, infection, etc. This also explains why mast cell tumors tend to be swollen, inflamed, ulcerated and itchy. Often a “blush” or skin redness around the tumor is apparent (Darier’s sign). Shar-Pei have a higher than normal population of mast cells in their subcutaneous tissue which may partially explain the frequency and aggressiveness of these tumors in our breed. Due to the increased mucin in the subcutaneous tissues of Shar-Pei spread of mast cells may occur more easily as well — the mucin may also hinder the identification of the tumor margins and thus the complete surgical removal of mast cell tumors. There appears to be an inherited or genetic aspect to mast cell cancer as well as it appears more often in some lines of Shar-Pei. There also seems to be a connection between eosinophilic granulomas and mast cell cancer in some individuals. I have removed masses which on histopath read out as eosinophilic granulomas and recurred as mast cell tumors. The ultimate cause of this type of cancer is unknown. It is the most common skin tumor in dogs accounting for about 20% of all reported skin tumors. Dogs with mast cell tumors have increased levels of circulating histamine, which may lead to GI ulcers and allergic reactions.

2. **SIGNS:** Owners may report seeing a mass that grows and shrinks repeatedly – this is usually due to local histamine release that leads to intermittent swelling. Some dogs have a recent rapid tumor growth while others have a tumor that has been present and unchanged for months to years. There is not one characteristic appearance for mast cell tumors – often skin nodules are reddened, itchy and ulcerated. These can be confused with histiocytomas, a benign growth which often regresses on its own in 4-8 weeks and which are often seen in Shar-Pei at any age. In Shar-Pei cutaneous mastocytosis may be seen in which large areas of skin are involved without an actual tumor being present – often this is confused with allergic skin disease or demodecosis. The importance of fine-needle aspiration and cytology cannot be over-emphasized. Subcutaneous nodules (under the skin) can be confused with lipomas, benign fatty tumors.

3. **DIAGNOSIS:** Any lump or bump on a Shar-Pei is suspicious. Mast cell tumors are often confused with histiocytoma, a benign tumor of the skin which also has a high incidence in the Shar-Pei. If the mass is large enough a fine-needle aspirate may be done to identify the mast cells. Often the tumor must be identified after it is removed. A particularly troublesome variation of mast cell tumor known as AGRANULAR SPINDELOID MAST CELL or ANAPLASTIC MAST CELL is seen in the Shar-Pei and is characterized by mast cells with few or no granules. This is a very aggressive form of mast cell and can be confused with other tumor types. The most commonly used grading system for mast cell has a Grade 1 which indicates a well-differentiated mast cell type and is considered least malignant, Grade 2 which is an intermediate type and which I consider malignant in the Shar-Pei and a Grade 3 which is an undifferentiated type of mast cell and definitely considered malignant.

4. **TREATMENT:** Surgical removal of the tumor with wide normal margins is the current recommended treatment. Obviously the smaller the tumor the more easily this is accomplished. Location of the mass also determines how successful surgery will be. I often recommend referral to a veterinary oncologist (cancer specialist) or a veterinary cancer center. At the cancer center there is usually a group consisting of a veterinary surgeon, veterinary oncologist and often, radiation treatment facilities. The chemotherapeutic approach for mast cell cancer is not well worked out at this time and is an area of active research. Mast cells are radiation-sensitive and radiation therapy is often used as an adjunct to surgery. The Shar-Pei owner must decide early on how aggressive an approach they will seek. Local recurrence and spread of mast cell cancer often occurs within 4-6 months after surgery alone. The prognosis in the Shar-Pei is guarded to poor. I have seen mast cell cancer in Shar-Pei as young as 10 months. Chemotherapy often includes prednisolone in
combination with other agents. Currently tyrosine kinase inhibitor therapy appears to be useful in the treatment of mast cell cancer.

5. **MASTOCYTOSIS:** This is a form of mast cell cancer which is systemic and involves internal organs such as the liver, spleen, lymph nodes and GI tract. This can have a much poorer prognosis.

6. **PARANEOPlastic SYNDROME:** This term denotes systemic signs which accompany certain types of cancer. The inflammatory response which often accompanies mast cell cancer can result in GI tract ulceration with vomiting and diarrhea, often with blood, as a consequence. Sometimes excessive manipulation of a mast cell tumor can result in massive degranulation of the tumor cells which can lead to a life-threatening systemic shock reaction. Most common is the localized swelling, draining and itching at the tumor site.

7. **PROGNOSIS:** Mast cell tumors have extremely variable biologic behavior. Some are relatively benign and curable with local excision while others may be very aggressive, spread rapidly (metastasis) and are fatal. Sites for metastasis include regional lymph nodes, spleen, liver, bone marrow and skin – they rarely involve the lung. Negative prognostic factors:

   - Recent, rapid growth
   - Deep, fixed mass
   - Systemic signs: tarry stools, vomiting, etc.
   - Tumor location – poorer prognosis for tumors on the muzzle, inquinal/preputial areas and mucocutaneous junctions (mouth, anus, nail beds)
   - Regional lymph node metastasis
   - Internal spread
   - Histologic features – high grade tumor (grade 3), high mitotic index (>5 mitotic figures/10 hpf), presence of c-kit mutation, high Ki-67 score (>1.8).

Ultrasonography can also be used to evaluate abdominal organs (spleen, liver, GI tract and lymph nodes for metastatic mast cell disease

**New Information:**
Research conducted over the last several years has concentrated on the genetic aspects of mast cell cancer. KIT is a receptor protein located on mast cells which is encoded by the proto-oncogene c-kit. A gene normally encodes for a protein product which performs a specific function in the body and in many genetic diseases a gene mutation occurs which results in no protein being produced or an abnormal protein product which is either non-functional or has an abnormal function. In normal mast cells KIT signaling is critical for the normal development and function of mast cells. Mutations in c-kit result in KIT dysregulation which may promote uncontrolled growth or survival of mast cells. These mutations in c-kit have been discovered and consistent of tandem duplications in exons 11 and 12 of the gene. These exons encode for the juxtamembrane domain which prevents activation of KIT. It acts as an “on-off” switch if you will. These mutations cause a continuous “on” signal for KIT and appear to be associated with more aggressive mast cell tumors. Another study has demonstrated loss of intron 11 which is the region between exon 11 and 12 which occurs in canine mast cell tumors. This suggests that canine mast cell disease is probably the result of several different mutations in the c-kit region.

Additional research has looked at the serine proteases α-chymase and tryptase which are selectively concentrated in secretory granules of mast cells. These serine proteases may potentially serve as markers of the biological aggressiveness of mast cell tumors 5.


As a direct result of some of the above research projects some therapeutic trials have been initiated. Since KIT is classified as a receptor tyrosine kinase it can be inhibited by agents called kinase inhibitors. Several of these drugs are in the pipeline. One has been developed for humans called Gleevac® (STI571) which blocks the ATP binding site of KIT and inhibits KIT signaling. Liver toxicity has been a problem in animals with this drug. Another class of kinase inhibitors called the indolinone kinase inhibitors (SU5416, SU6668) are currently being studied in humans. These agents are capable of disrupting the function of all forms of mutant KIT. Remissions of up to 6 months have been induced by these agents in some cases of mast cell cancer in dogs but relapses occur 6.


Another recent article has looked at mast cell cancer and plasma histamine concentrations. Mast cell granules contain histamine, heparin and proteolytic enzymes. Release of these granule substances can cause gastroduodenal ulceration/perforation, delayed wound healing, hypotensive shock, local ulceration/swelling and coagulation abnormalities. Hyperhistaminemia is a major factor contributing to gastroduodenal ulceration and perforation. Histamine release from mast cell tumors can occur due to spontaneous release, aggressive manipulation (especially during surgery), chemotherapy and radiation therapy. Plasma histamine concentration is one factor related to mast cell disease progression. It also appears related to tumor dissemination. Up to 80% of dogs with progressive mast cell cancer have gastroduodenal ulceration. Lastly, dogs that don’t respond to H2 blockers have marked hyperhistaminemia. This study concludes that plasma histamine concentrations may provide useful diagnostic, prognostic and therapeutic information 7.


The drug company Pfizer has plans to release a tyrosine kinase inhibitor for the veterinary market called Palladia® in late 2009 or early 2010. It will be labeled for use in mast cell cancer in the dog. No further information is available at this time.

Another potential modality in the treatment of mast cell cancer involves the use of mast cell stabilizers. One such drug is cromolyn sodium (Gastrocrom®). Another drug which inhibits mast cell histamine secretion is pentosanpolysulfate (Elmiron®, Cartrophen®). This is a synthetic, sulfated polysaccharide that has been approved for the treatment of interstitial cystitis (IC) – it may help replenish the defective glycosaminoglycan layer in the bladder in this condition. A research paper indicates pentosanpolysulfate has a powerful dose-dependent inhibitory effect on mast cell release of histamine.

8. Chiang G, Patra P, Letourneau R, Jeudy S, Boucher W, Green M, Sant GR, Theoharides TC. Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis. Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, Massachusetts, USA.

Palladia® (toceranib phosphate) has been around for about 3 years now and here are some insights from the specialists who use it:

1. Palladia® will be effective only in Grade II or Grade III mast cell tumors that are positive for the c-Kit
gene mutation. It is important when a mast cell tumor is removed that it be tested for this genetic mutation. Only 28% of mast cell tumors are positive for this mutation.

2. Palladia® should be used with the same precautions as any other chemotherapeutic drug. It can be nephrotoxic, may cause pancreatitis, low serum albumin levels, anemia, low white blood cell counts, etc. Dogs should be seen weekly for the first 6 weeks with CBC, blood panel and urine samples checked. The dosage of the drug should be adjusted or the drug discontinued if any of these side-effects are seen.

3. Often it is best to start with a dosage about 25% less than the original dosage proposed by the manufacturer and often other drugs are added such as prednisone, antihistamines and H2-receptor antagonists such as Tagamet-HB®, Pepcid-AC® and others to minimize side effects.

4. Another drug called Masivet® (masitinib) is currently in clinical trials in Europe. This drug appears to have fewer side effects than Palladia®. It is now available in the U.S. as Kinavet®

5. I have seen some promising results with the use of Palladia® in some of the mast cell cases I’ve personally referred to oncologists who have used it. It is an oral medication and can be given by owners at home – a distinct advantage over other chemotherapies.

Masivet® (Kinavet-CA1®)
- Masivet® is the brand name for the tyrosine kinase inhibitor masitinib.
- It specifically targets stem cell receptor c-Kit, PDGFR α and β, and LYN.
- Particularly effective in controlling the proliferation, differentiation and degranulation of mast cells.
- Useful in the treatment of mast cell dysfunctions.
- In mast cell cancer treatment it is only used if the presence of a mutated of the receptor protein c-Kit in the tumor has been confirmed. Excessive action of c-Kit results in uncontrollable mast cell proliferation. Masivet® blocks receptors for c-Kit.
- Dogs on Masivet® took longer for the tumor to get worse (median of 241 days in treated dogs vs. median of 83 days in untreated dogs).
- Survival rates at 12 and 24 months were significantly improved in dogs receiving this drug.
- Tumor response at 6 months was predictive of long-term survival at 12 and 24 months.
- First-line treatment with masitinib was more effective than placebo regardless of whether a c-kit mutation was present. Dogs that had received other therapy prior to masitinib, however, only responded if the c-kit mutation was present.
- Masitinib effective in dogs with metastases.
- Also significantly reduces the emergence of nodal and visceral metastasis.
- Prevents the proliferation of tumor mast cells
- Inhibits the phosphorylation of PDGF-α and β receptors as well as PDGF-dependent cell proliferation.
- Inhibits mast cell degranulation modulates inflammatory and immune responses.
- Tablet sizes = 50mg. and 150mg.
- Common side effects are diarrhea, vomiting and alopecia.
- Dose is 12.5 mg/kg once a day.
- Kinavet-CA1® -- ABScience (in the United States)
- Inhibits LYN kinase activity. Lyn has been associated in certain forms of TKI resistance and is associated with several different cancers.
- Side-effects include non-regenerative anemia, decreased white blood cell counts, protein-losing nephropathy
- Particularly effective in controlling the proliferation, differentiation and degranulation of mast cells.
- Useful in the treatment of mast cell dysfunctions.
- They play a key role in chronic inflammatory diseases such as allergies, atopic dermatitis, asthma and arthritis
- Kinavet-CA1®Tablet sizes = 50mg. and 150mg.

More mast cell stuff:
• c-kit is a receptor tyrosine kinase for stem cell factor (SCF). Stem cell factor stimulates mast cell growth.
• Mutations in c-kit are: internal tandem duplications (ITD) within exons 11 and 12 of the c-kit gene. This is known as the exon 11 mutation.
• When SCF binds to unmutated c-kit, the cytoplasmic portion of the receptor undergoes autophosphorylation. In the presence of the exon 11 ITD, the receptor is constitutively phosphorylated, regardless of whether SCF is present or not. The presence of the mutation is directly responsible for the uncontrolled proliferation of mast cells.
• Other c-kit mutations: 12-base pair ITD in exon 8, single base pair change in exon 9, additional single base changes and rare deletions and insertions detected in exon 11 and exon 17.
• Current methodology will not detect single base pair changes (false negatives?).
• The standard methodology requires approximately 10% of the cells in the sample to be mast cells – not useful for detecting mets in draining lymph nodes or for residual disease detection.
• First-line treatment with masitinib was more effective than placebo regardless of whether a c-kit mutation was present. Dogs that had received other therapy prior to masitinib, however, only responded if the c-kit mutation was present.
• In another study, dogs with recurrent mast cell disease responded better to Palladia if they carried the exon 11 c-kit mutation than if they did not.
• c-kit mutations can be used as a tumor fingerprint – determines if recurrent mast cell tumors are from the same clone (the same mutation).
• Possibility of creating tumor-specific PCR primers based on the mutated sequence which could detect distant metastases and the presence of neoplastic cells in the blood and can even be used to quantify tumor cells.
• c-kit mutations present in gastrointestinal stromal cell tumors (GISTs) also.
• Detection of c-kit mutations in mast cell tumors is now routinely used for prognosis and guiding treatment. Most commonly, mutation status is determined together with immunohistochemical staining to examine proliferation markers and the cellular location of c-kit. These factors help establish prognosis and the need for additional therapy.

I realize much of this new information will mean little to the reader but four points need to be made. First, the Chinese Shar-Pei Club of America Charitable Trust has been actively involved in funding much of this research in mast cell disease. I believe this function of the Charitable Trust is critical for our breed and I believe your continued donations to the Trust are critical for our breed as well. You won’t see breakthroughs in cancer research unless you have funding of that research. Second, there is a great deal of information sharing in the scientific community concerning cancer research. Much of the work I share here has application to human cancer as well. Third, much of this research information is applicable to other cancers as well. This means that progress in the studies of other cancer types will be much more rapid. Lastly, as dog enthusiasts, understanding the genetics of cancer will allow us to develop tests and breeding programs to avoid those types of cancer which may have a hereditary aspect to them.


Dr. Linda Tintle and Dr. Jeff Vidt maintain web sites full of information about the Chinese Shar-Pei. They can be found at www.wvc.vetsuite.com and www.drjwv.com. Dr. Vidt has a “Vets Only Section” of his web site. Vets can click on his link to find instructions on how to get into the area for vets only.