

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, and a number of other substances. The release of these vasoactive molecules cause inflammation, itching, edema, and attract other 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 and itchy. 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. The ultimate cause of this type of cancer is unknown.
- 2. 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** is seen in the Shar-Pei and is characterized by mast cells without 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.
- 3. 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.

4. **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.
5. **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.

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 consist 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.

1. London CA, Chien MB, Pfeiff J, Downing S, Grahn RA. Genes, Dogs and Cancer: Emerging Concepts in Molecular Diagnosis and Therapy. Conference May, 2001.
2. Reguera MJ, Ferrer L, Rabanal RM. Evaluation of an intron deletion in the *c-kit* gene of canine mast cell tumors. *Am J Vet Res* 63.9:1257-1261.
3. Downing S, Chien MB, Kass PH, Moore PF, London CA. Prevalence and importance of internal tandem duplications in exons 11 and 12 of *c-kit* in mast cell tumors of dogs. *Am J Vet Res* 63.12:1718-1723.
4. Dank G, Chien MB, London CA. Activating mutations in the catalytic or juxtamembrane domain of *c-kit* in splenic mast cell tumors of cats. *Am J Vet Res* 63.8:1129-1133.

Additional research has looked at the serine proteases α -chymase and trypsin 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.

1. Serine Proteases in Mast Cell Disease. Timothy M. Fan, DVM, DACVIM, *Proceedings of the 20th Annual AVCIM Forum*, Dallas TX, May 2002, pages 414-415.

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.

1. Kinase Inhibitors in Cancer Therapy. Dr. Cheryl London, DVM, PhD, DACVIM. *Proceedings of the 20th Annual ACVIM Forum*, Dallas TX, May 2002, pages 436-438.

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.

1. Ishiguro T, Kadosawa T, Takagi S, Kim G, Ohsaki T, Bosnakovski D, Okumura M, Fujinaga T. Relationship of Disease Progression and Plasma Histamine Concentrations in 11 Dogs with Mast Cell Tumors. *J Vet Intern Med* 2003; 17.2:194-198.

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.

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