Genetics Likely Cause of Mast Tell Tumors in Labradors
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Mast cell tumors (MCTs) occur more frequently in canines than any other species. While many are benign, MCTs are among the most common malignant canine tumors, affecting as many as 20 percent of dogs.

The most common canine skin tumor, MCTs also can occur in the liver, spleen, intestines and bone marrow, and can metastasize to other parts of the body. The tumors usually develop in dogs 8 to 9 years old – both male and female – but also have been reported in very young dogs.

Labrador Retrievers are one of several breeds at increased risk for MCTs. In a recent survey of 124 dogs with MCTs, Labrador Retrievers, Golden Retrievers and Chinese Shar-Pei were the most commonly affected breeds. Labrador Retrievers represented about 14 percent of all dogs in the study.

Labrador Retrievers' susceptibility likely is genetic, says Cheryl A. London, DVM, PhD, associate professor in the Department of Veterinary Biosciences at The Ohio State University. "It's really important if you have a breed at risk that you check your dog frequently for any new masses", she says.

Not Always Fatal

"Not all dogs that get mast cell tumors die of their disease," London says. "Many of them are benign or they are completely cured by surgical removal." She estimates that 60-70 percent are cured with appropriate medial care.

Normal mast cells are present in all tissues, especially the skin, lungs and intestines. Part of the immune system, mast cells help fight infection and are responsible for allergic reactions. But when genetic mutations cause the cells to grow uncontrollably, tumors develop.

The cancer is unpredictable and can be extremely aggressive; therefore, every MCT should be treated as potentially malignant, says London. MCTs can mimic other tumors, making it impossible to identify them simply by appearance, and those that originate in the gastrointestinal tract, liver, spleen, bone marrow, muzzle/oral cavity, and nail bed are more likely to be malignant.

MCTs are frequently seen at sites of inflammation. Since mast cells can release histamine, secondary gastrointestinal ulceration occurs in as many as 83 percent of dogs. Consequently, signs of MCT may include vomiting, anorexia, gastrointestinal bleeding (recognized as blood, or a "coffee-ground" appearance, in vomitius or dark tar-colored stools) and abdominal pain.

About half of skin MCTs occurs on the trunk and perineal region, 40 percent on the limbs and 10 percent on the head and neck. Roughly 10-15 percent of dogs have multiple tumors. Slow-growing MCTs – those present for at least six months – are more likely to be benign, while rapidly growing large tumors are more likely malignant.

Research has found that 83 percent of dogs with tumors present for longer than 28 weeks prior to surgery survived for at least 30 weeks, compared to only 25 percent of dogs with tumors present for less than 28 weeks. Most dogs surviving for more than 30 weeks after surgical removal of an MCT appear to be cured; however some incompletely excised MCTs can recur.

There are five states of MCT development, ranging for a single tumor confined to the skin to multiple tumors and metastasized tumors involving the blood or bone marrow. Fine-needle aspiration of an MCT can lead to diagnosis and ultrasound can help pinpoint a tumor's location. However, only biopsy can determine the grade of the tumor, which indicates the histological appearance of the tumor and ranges from a benign Grade I to a malignant Grade III.

If a tumor is surgically removed, one study showed that 83 percent of dogs with a Grade I MCT, 44

percent of dogs with Grade II and 6 percent of dogs with Grad III were living 1500 days after surgery. In another study, 100 percent of dogs with a Grade I MCT, 44 percent of dogs with Grade II and 7 percent of dogs with Grade III were living two years after surgery. Radiation and chemotherapy may be used following surgery. Even if the MCT is not completely removed, 90 percent of dogs that received radiation following surgery for Grades I and II MCTs survived for at least three years.

Looking at C-Kit Mutations

London's research focuses on a gene called c-kit, which codes for the protein Kit. In dogs, c-kit mutations – called internal tandem duplication – lead to excessive Kit signaling and loss of growth control, contributing to tumor development. Thirty percent to 50 percent of malignant MCTs have Kit mutations, indicating that these mutations play a role in this disease.

In conjunction with Pfizer, a pharmaceutical company, London and a team of researchers tested a kinase inhibitor to block Kit function, disrupting the growth of malignant mast cells. A clinical trial of the inhibitor showed success, with tumor reduction occurring in 11 of 22 dogs with MCTs. Despite the success, London does not know whether Pfizer intends to market the inhibitor.

"We are taking a more aggressive approach to look for new targets for intervention," she says. "We've developed a technique to grow normal mast cells from bone marrow. This means that we can readily have available populations of normal cells – which has been a big problem in the past – so that we can look at differences in gene expression between the normal mast cells and the malignant mast cells." The work being done in conjunction with the National Cancer Institute with support from the AKC Canine Health Foundation, which includes funding from Purina and the American Kennel Club.

In addition, London recently completed work evaluating the role of mitotic index as a prognostic indicator for MCTs. "One of the big problems has been predicting which mast cell tumors are going to be biologically aggressive," she says. "We haven't had a good indicator of which ones are likely to go bad and which ones are not. The mitotic index is a very simple tool: It's a measure of cell proliferation. It allows you to identify those tumors that are rapidly growing."

This study examined 100 MCTs and found that mitotic index was a very strong predictor of survival time for dogs with both Grade II and Grand III MCTs. "It looks like it's very statistically significant," London says.

As with human cancer, early detection is key. "Any dog should be checked frequently for any new masses," London advises. "And immediately follow up. Don't wait."

MCT Samples Needed from Labradors

Researches are collecting blood samples from Labrador Retrievers with mast cell tumors (MCT) as well as from older unaffected dogs to compare the genome profiles of affected and healthy dogs. Their goal is to find genes contributing to the genetics of the disease in Labradors. Cheryl A. London, DVM, PhD, associate professor in the Department of Veterinary Biosciences at The Ohio State University, is leading the project together with collaborator Kerstin Lindblad-Toh, PhD, co-director of the Genome Sequencing and Analysis Program at the Broad Institute of MIT and Harvard. For more information contact:

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Mast Cell Tumors by Grade

These grades of mast cell tumors (MCTs, with each higher grade representing a more serious condition, are found in dogs:

- **Grade I: Benign.** Thirty percent to 55 percent of MCTs are Grade I. Complete surgical removal usually is curative, with 75-90 percent of dogs cured following therapy. If surgical excision is incomplete, a wider excision or radiation therapy is recommended.
- **Grade II: Benign or malignant.** Twenty-five percent to 45 percent of MCTs are Grad II. These tumors have invaded the tissue below the skin (dermis) and have the ability to spread. Mean survival time is 28 weeks after surgical removal; however, radiation therapy following incomplete excision can cure more than 80 percent. Chemotherapy may be recommended for aggressive Grade II tumors.
- **Grade III: Malignant.** Twenty percent to 40 percent of MCTs are Grade III. Metastasizes early on, with a mean survival of 18 weeks with surgery; however, post-operative chemotherapy and/or radiation therapy might prolong survival.