

Acute Myeloid Leukemia

The mutational landscape in dogs with acute myeloid leukemia

by Dr. Tracy Stokol BVSc PhD (Cornell University)

On behalf of co-investigators: Dr. Dorothee Bienzle (University of Guelph),
Dr. Nora Springer (University of Tennessee), Dr. Kristina Meichner (University of Georgia),
Dr. Nathan Montgomery (Tempus)

Acute myeloid leukemia (AML) is a highly aggressive, rapidly progressive tumor that arises in the bone marrow. Leukemia occurs when an early precursor cell in the marrow develops one or more defects (mutations) in its genes. Then, instead of making normal myeloid cells that circulate in the blood, such as red blood cells, white blood cells and platelets, the mutated precursor churns out tumor cells. These tumor cells start to replace the normal cells in blood and bone marrow, resulting in low blood counts, such as anemia (Figure 1).

The tumor cells can also spread via the blood to other tissues, such as the liver and spleen. Animals affected with AML eat less or go off their food and can become weak and lethargic. Because white blood cells and platelets are important for fighting off bacterial infections and making blood clots, respectively, they may also suffer from fever and bruising (Box 1). Although AML is less common than lymphoma, the more widely known blood cancer that arises in lymph nodes versus the bone marrow, AML is usually more aggressive and difficult to treat than lymphoma. We also do not have many treatment options for affected dogs, using a limited number of older traditional drugs that don't always work well. As a result, most dogs with AML are humanely put down or die within days to weeks of diagnosis, even with treatment.

People, including young children, also suffer from AML and the leukemia shows similar behavior and response to traditional therapy as it does in dogs. However, advances in genetic testing and detection of mutations in humans has led to better classification of the different types of AML, allowed for improved prediction of responses to treatment and overall prognosis, and resulting in the development of new drugs that target specific mutations and subtypes of AML. Indeed, testing for a panel of mutations has now become a routine part of the diagnostic workup of human patients with AML. However, unlike people, we currently know very little about the genetic landscape of AML in dogs, which is the goal of our multi-institutional study. Our ultimate hope is that we will use the knowledge of the genetic mutations in AML in dogs to better classify the leukemia, provide more accurate predictions of how the tumor may behave, and treat dogs with more effective drugs that will

Symptoms of AML
Off food or anorexic
Tired or lethargic
Weakness
Vomiting or diarrhea
Weight loss
Increased respiratory rate
Increased heart rate
Fever
Bruising

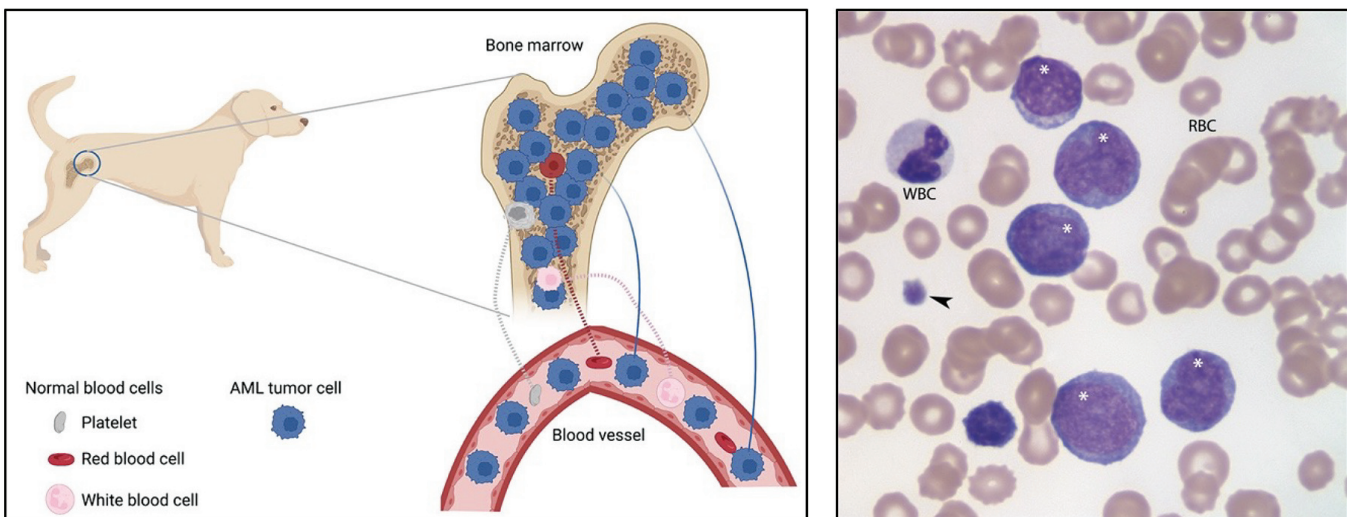


Figure 1: In AML, the cancer arises in the bone marrow and replaces normal blood cells (platelets, red blood cells, white blood cells), such that fewer normal cells are present in blood (left panel; created with Biorender.com). **Right panel:** In this image of the blood of a dog with AML, there are many tumor cells (white asterisks) with fewer red blood cells (RBC), white blood cells (WBC) and platelets (arrowhead) than normal.

¹ Please note that the gene mutations in AML are acquired after birth and appear during the dog's lifetime and are not inherited nor passed onto their puppies.

How you can help

If your veterinarian suspects your dog may have an acute leukemia, either you or your veterinarian can contact Dr. Stokol via the Cornell Clinical Trials website (see below)

help them cope with the disease and lengthen their lives.

In this study, which is being supported by the Canine Health Center at Cornell University and the Canine Health Foundation of the American Kennel Club, we plan to perform in-depth genetic sequencing of the

tumor cells in dogs with AML. We hope to enroll 50 dogs with AML in the next two years. To be eligible for the study, an acute leukemia must be first diagnosed.

Because the symptoms of AML are not specific and can be seen with other diseases, the cancer is initially detected by a blood test, called a complete blood count (CBC) or hemogram. A CBC is routinely done by veterinarians in most sick dogs. If the dog has an acute leukemia, the test will show the presence of tumor cells in blood, typically along with low blood counts of normal cells (Figure 1). However, even if a dog has a leukemia, it does not mean it is an AML since there are other types of leukemia that affect dogs, although they are less common than AML. Thus, as part of this study, we will perform additional specialized tests on the dog's blood to confirm the diagnosis of AML. At the same time, we will obtain DNA from the blood for genetic testing of the cancer. We will also need to collect a sample of normal DNA from healthy cells in the dog's mouth by gently rolling a special swab against the inside of the mouth. Once you or your veterinarian contacts us, we will send the swabs and consent form along with a prepaid shipping label to your veterinarian to obtain the samples needed for the study.

The investigators of the study are veterinary clinical pathologists and a human pathologist, all of whom have

expertise with leukemia in dogs or people. The investigators will meet regularly to decide which dogs have AML and should be included in the study. Then, genetic sequencing will be done on DNA extracted from tumor cells in blood and normal cells from the mouth, and the results analyzed to identify mutations. We will compare the normal DNA to the tumor DNA to be sure that any mutations we are seeing are specific for the tumor and not just random genetic changes that are not associated with cancer.

We expect to find that subsets of dogs will have common genetic mutations, allowing the dogs to be grouped on the basis of their genetic abnormalities. In the future, this information could be used to identify new drugs to treat dogs with AML and track how dogs with certain mutations do after treatment. We hope that testing for the genetic mutations will become commonplace and part of the routine diagnostic evaluation of dogs with AML, just like we do for humans. If your veterinarian is suspecting that your dog may have acute leukemia, we recommend that you contact Dr. Stokol for more information on how to participate in the study.

For more information on the study, please check out these urls:

<https://www.vet.cornell.edu/news/20211129/catching-human-treatments-canine-aml>

<https://www.vet.cornell.edu/hospitals/clinical-trials/sequencing-genes-dogs-acute-myeloid-leukemia>

<https://ovc.uoguelph.ca/news/node/702>

What we need

- Fresh blood sample
- Mouth swabs
- Your consent
- Your dog's medical record