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MEDIATIONS ON LYMPHOMA IN DOGS AND CATS

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HOW FREQUENTLY DOES LYMPHOMA OCCUR IN DOGS AND CATS?

Examining the literature will only give us an approximation for a number of reasons. Historical estimates put the number of cases of lymphoma in dogs to be between 6 and 30 cases/100,000. In 2002 the estimated population of dogs in the United States was 60.7 million and this suggests a range of 3,342 to 18,210 cases of canine lymphoma annually. Lymphoma in cats represents 1/3 of all malignancies and early surveys suggested an occurrence rate of 16 to 200 cases/100,000. In 2002 the estimated population of cats in the United States was 76.8 million so this suggests an annual prevalence of between 122,880-153,600 cases of lymphoma in cats. The effect of vaccination on the prevalence of lymphoma in cats is unknown.

In examining the literature the terms incidence and prevalence are frequently encountered and they are often inappropriately used interchangeably. The term Incidence refers to the frequency of a disease in a population over a defined period of time divided by the number of individuals in the exposed population. The term prevalence refers to the frequency of a disease in a population occurring at the same time divided by the number of individuals in the exposed population.

WHAT IS THE ETIOLOGY OF LYMPHOMA IN DOGS AND CATS?

Recent literature raises more questions than answers about etiology. Simply put, the etiology of lymphoma in dogs is unknown. Older literature suspected a viral etiology because reverse transcriptase activity was found in tumor tissue, however no viral etiology has ever been documented. There have been several reports that first seemed to incriminate a particular etiology but were later proved to be false. Among these false reported etiologies are exposure to magnetic fields created by electric transmissions lines and electric currents.

Reports of lymphoma occurring in related pure breed dogs suggests a role for genetics and some breeds such as Golden Retrievers are often cited in studies as being prone to develop lymphoma. Dogs with lymphoma have been shown to have a chromosomal segregation error that may promote or not interfere with malignant transformation. Interestingly, the canine MCY gene has the same structural organization as the human MYC gene and other genes such as the IGH, TCRB, and BCL2 genes of dogs show organizational similarities to the equivalent human genes. Activation of the MYC and BCL2 genes from chromosomal translocations has been shown to be a major pathway in the development of non-Hodgkin’s lymphoma in humans. A similar mechanism may occur in dogs that develop lymphoma. Another possible similarity in etiology between dogs and humans with lymphoma is the rarity of c-N-ras mutations in either dogs or people with lymphoma.

The only documented cause of lymphoma in cats is FeLV. In surveys done in the 1970’s and 1980’s approximately 70% of cats with lymphoma in the United States and Western Europe were FeLV positive. In a very recent study from the Netherlands only 4 of 54 cats were FeLV positive. Reports from the 1980’s suggested that 75%-85% of cats with mediastinal lymphoma would test positive for FeLV, but in this study from the Netherlands only 18.8% of cats with mediastinal lymphoma were FeLV test positive. These findings raise questions about the exclusive role of FeLV in causing lymphoma in cats especially in geographic areas with low FeLV prevalence like the Netherlands.

Fleas are an important vector in the transmission of a number of diseases, such as bacteria and rickettsiae and perhaps FeLV as well. A recent investigation of the role of the cat flea (Centocephalides felis) in the spread of FeLV raised several interesting issues regarding transmission of FeLV. In this study, FeLV RNA could be detected in fleas and in their feces after being fed FeLV positive cat blood for 24 hours. This finding raises the possible risk of a healthy cat scratching flea feces into its skin as the result of pruritic flea bites or while fighting with other cats. It also raises the possibility of direct transmission of FeLV through the flea and flea bites.

ARE LATENT FELV INFECTIONS REALLY THE CAUSE OF “FELV ASSOCIATED DISEASES?”

Latent FeLV infections in which proviral DNA is present in a non-replicating form in bone marrow derived myelomonocytic progenitor cells have been suspected to be associated with diseases such as lymphoma, leukemia, and cytopenias. Latent FeLV infections are undetectable with ELISA or IFA testing. Many cats with what are regarded as “FeLV associated diseases,” are test negative on traditional FeLV assays. Polymerase Chain Reaction (PCR) is advocated by some as an alternative to ELISA testing and as a means to detect FeLV proviral DNA in bone marrow of cats suspected of having latent infection. Recent studies of PCR for this purpose has raised questions related to historical assumptions.

In a study that included 16 cats suspected to have latent FeLV infection, PCR, ELISA, and IFA on bone marrow were performed and compared. These cats had disorders such as pancytopenia, leukopenia, neutropenia, non-regenerative anemia, lymphoma, and different types of leukemia that have historically been attributed to latent FeLV infection. In this study 12 of the 16 cats were negative on serum ELISA, blood and bone marrow IFA, and blood and bone marrow PCR. None of the 16 cats were test positive on bone marrow PCR alone. It appears that persistent or latent FeLV infection is not always present (detectable?) in conditions classically associated with FeLV. This is an important observation because it forces the conclusion that FeLV may not always be the cause of what have been previously described as FeLV associated diseases.

WHICH CLASSIFICATION SCHEME FOR LYMPHOMA SHOULD I USE?

Unfortunately, there still is no universal standard among veterinary pathologists by which a lymphoid tumor is classified. Clinicians in North America may receive histopathology reports from pathologists that diagnose lymphoma and classify it according to the Rappaport, Kiel, NCI-WF, or REAL systems (the Kiel system is the standard in Europe). On the other hand, clinicians in North America are just as likely to receive reports that simply diagnose lymphoma and make no effort at providing additional
classification data. However, the classification scheme developed by the National Cancer Institute called the Working Formulation (NCI-WF) can be applied to dogs and cats with lymphoma and is a clinically useful. The NCI-WF uses mitotic index and natural rate of progression to classify tumors as low-, intermediate-, or high-grade. High-grade tumors are populated by large lymphoblasts with abundant cytoplasm and high mitotic activity. High-grade tumors are rapidly progressive clinically and can be either B- or T-cell type. Low-grade tumors are populated by small cells with a low mitotic rate. Low-grade tumors are more slowly progressive clinically and are usually B-cell type.

The American College of Veterinary Pathologists has established a working group to examine and adapt the current (2001) World Health Organization (WHO) classification scheme that is recommended for human lymphoid tumors. The WHO system considers the clinical presentation and disease progression together with the immunophenotype, anatomic site, morphology, and cytogenetics for classifying lymphoid tumors. The entire topic of the histologic classification of lymphoid malignancies in veterinary medicine remains unsettled, and is in the process of transition.

WHAT IS THE ROLE OF IMMUNOPHENOTYPING IN THE DIAGNOSTIC WORK-UP OF LYMPHOMA?

Immunophenotyping refers to the use of monoclonal antibodies specific for differentiation antigens that are expressed by lymphocytes and accessory immune cells to identify them as either T or B lymphocytes. Immunophenotyping is a complement to conventional assessment of lymphoma that is based on morphology. Immunophenotyping can be performed on a variety of specimens, but it is usually performed on unfixed air-dried blood smears, cytological preparations, and fresh tissue that have been snap frozen and sectioned. However, a few mAbs have been developed that allow detection of cellular antigens in formalin fixed tissues. Panels of different monoclonal antibodies (mAb) are applied to the specimens to be examined, and the resultant patterns of expression allow for identification and classification of different cells (T and/or B lymphocytes). This approach has lead to a common nomenclature for antigen expression by a species that are known as “Cluster of Differentiation” antigens or CD antigens depending on how the cells stain with antibody. Examples of mAbs used are CD-3 that is expressed on the surface of mature T-lymphocytes, CD-4 that is expressed by T helper cells, CD-8 that is expressed by T cytotoxic cells and some NK cells, CD-79a that is expressed by T lymphocytes and CD-45 that is expressed by B cells in formalin fixed specimens. In dogs 70-75% of lymphomas are B-cell type, 20-25% are T-cell tumors, and <5% are non-B/non-T tumors. T-cell lymphoma is associated with early treatment failure. In cats >95% of lymphomas are B-cell in origin and <5% are T-cell tumors. The only clinical value of identifying patients with T-cell type tumors is in recognizing their poorer prognosis and perhaps selecting a more aggressive chemotherapy protocol.

IS THERE A RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE IN CATS AND LYMPHOMA?

Distinguishing between inflammatory bowel disease and lymphoma can be a challenge for the clinician, and at times, the pathologist. There has been considerable speculation that in some cases chronic inflammatory bowel disease in cats may be an antecedent event to lymphoma. The presumed relationship between alimentary lymphoma and inflammatory bowel disease is very interesting and perplexing. Although approximately 90% of lymphoma in cats are classified as intermediate or high-grade, two recent studies of gastrointestinal lymphoma in cats suggest that most cases of alimentary lymphoma is due to involvement with small, non-lymphoblastic lymphocytes that might not easily be recognized as malignant.

In one of these studies, 50/67 cats had lymphocytic versus lymphoblastic lymphoma with characteristics of epitheliotropism. The term "epitheliotropic" in alimentary lymphoma refers to the homing of malignant T-lymphocytes to the mucosal epithelium of the intestinal tract that is characteristic of this disorder. The clinical signs and histologic findings in epitheliotrophic alimentary lymphoma will vary widely. Very mild cases may be limited to small numbers of intramucosal small T-cell infiltrates, or extensive remodeling and replacement of normal intestinal architecture by pleomorphic large or anaplastic T-cells.

In the other report of epithelioptrophic lymphoma, 8/10 cats had involvement with small, but malignant lymphocytes, and the other 2/10 cats had involvement with intermediate sized malignant lymphocytes. Immunophenotyping of the cats in this study showed that all 10 cats had T-cell disease. This suggests that on the basis of morphology alone without the ability to perform clonal analysis, it may be extremely difficult to distinguish inflammatory bowel disease (small lymphocytes infiltrating the bowel) from epitheliotrophic lymphoma.

REFERENCES