A PRACTICAL GUIDE TO LEUKEMIA IN DOGS AND CATS

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SUMMARY

Although leukemias are relatively rare in dogs and cats, the diagnosis and classification of leukemia is important in establishing prognosis and treatment. The diagnosis of hematopoietic neoplasia in dogs and cats initially is based on results of a complete blood count (CBC) and examination of cell morphology in specimens from blood, bone marrow, and infiltrated tissues. However, morphologic evaluation of neoplastic hematopoietic cells has limitations, especially in identifying cell lineage of poorly differentiated cells.1 Adding cytochemical staining may be helpful, and allows application of human classification systems for some acute leukemias in domestic animals.1,2 A recent world-wide consensus classification of human hematologic malignancies incorporates genetic data, but this type of information is not yet widely available in veterinary medicine.3 Currently, immunophenotyping by flow cytometry is the preferred method of characterization of leukemic cells in human medicine.4 The recent development of monoclonal antibodies specific for leukocytes of different domestic animal species has made flow cytometry an available option for immunophenotyping neoplastic cells from domestic animals with hematologic neoplasia. In addition to providing information for diagnosis and classification, results of immunophenotypic analysis may provide clinically relevant information for prognosis and treatment of veterinary patients with hematologic malignancies.5-8

Introduction

Leukemia often is defined as the neoplastic proliferation of hematopoietic cells in the bone marrow, which typically results in circulating neoplastic hematopoietic cells. The bone marrow often is hypercellular due to proliferation of neoplastic hematopoietic cells. There is loss of orderly maturation of the neoplastic cells and normal hematopoietic cells may be decreased. In some cases, the neoplastic proliferation initially occurs in the spleen, with bone marrow involvement occurring later in the clinical course of the disease. There are two broad categories of leukemia based on cell lineage: myeloid and lymphoid. Leukemias also are classified as acute or chronic, based on cell morphology, differentiation of the neoplastic cells, and clinical course. The neoplastic cells in acute leukemias appear immature, whereas chronic leukemias are characterized by cells that appear more differentiated. In general acute leukemias have a more aggressive clinical course than chronic leukemias. Myeloid leukemias include neoplastic proliferation of erythrocytes, granulocytes, monocytes, and megakaryocytes. Multiple cell lines may be neoplastic if the neoplastic cells have multi-lineage potential. Acute myeloid leukemia (AML) is more common than chronic myelogenous leukemia (CML) in veterinary medicine. Lymphoid leukemias include acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).9 Clinical findings may be helpful in distinguishing acute and chronic leukemia, but are less helpful in distinguishing cell lineage.

The number of circulating neoplastic cells varies dramatically in dogs and cats with leukemia. Most commonly, the number of circulating neoplastic cells is greater than 5 x 10⁹/L (50,000/μL), and often is 100-300 x 10⁹/L. Occasionally, very few circulating neoplastic cells are present at the time of initial evaluation. In most dogs with acute and chronic leukemia, there also is anemia, neutropenia, thrombocytopenia, or some combination of cytopenias. Non-regenerative anemia, which usually is more
severe in acute leukemia compared to chronic leukemia, is present in most dogs with acute and chronic leukemia. Neutropenia is present in ~ 75% of dogs with AML and ALL, but is uncommon in dogs with CLL. Thrombocytopenia also occurs more commonly in dogs with AML and ALL, compared to dogs with CLL.\(^1\)

**Acute myeloid leukemia (AML)**

AML occurs primarily in young to middle-aged dogs and cats, but patient age is variable and includes very young and aged animals. Dogs and cats with acute myeloid leukemia frequently have a relatively acute onset of clinical signs related to peripheral cytopenias, or infiltration of the bone marrow and other tissue. Clinical signs include lethargy, weakness, pallor, bleeding, shifting leg lameness, and bone pain. Splenic involvement is common, involvement of the liver is variable, and peripheral lymph nodes may be mildly to moderately enlarged. Typical CBC findings include high numbers of circulating neoplastic cells that appear immature, moderate to marked non-regenerative anemia, neutropenia, thrombocytopenia, or some combination of cytopenias. The diagnosis of acute leukemia often is strongly supported by these changes in the CBC. Other laboratory changes are variable, depending on organ infiltration. The majority of cats with AML are infected with feline leukemia virus (FeLV). Response to therapy for AML in dogs and cats usually is minimal, and prognosis is poor.\(^9,10\)

AML in dogs and cats includes neoplastic proliferations of granulocytic, monocytic, erythroid, and megakaryocytic precursors. The classification scheme is complicated. Although it is important to distinguish between acute and chronic leukemia because of limited treatment options and poor prognosis for acute leukemias, the clinical relevance of distinguishing between AML and ALL and the further characterization of AML based on cytochemical stains and immunophenotyping remains to be determined in most veterinary species. This is different from AML in human beings, in which specific cell lineage may determine prognosis and lineage specific treatment.\(^9,10\) To classify AML, 200-500 nucleated cells in a bone marrow aspirate are differentiated to calculate a myeloid to erythroid (M:E) ratio and to determine the percentages of blasts and other cell types. Blast cell percentages are >20-30% of all nucleated cells. Cytochemical staining may provide helpful information, especially in differentiating granulocytic from monocytic acute leukemia. Monoclonal antibodies and chromosomal markers that have been developed to distinguish the various acute myeloid leukemias in human beings have either not been recognized in dogs and cats with AML or are not readily available for clinical patients.\(^9,10\)

**Chronic myelogenous leukemia (CML)**

Chronic myeloproliferative disease is the term used in the human classification system to comprise CML, chronic neutrophilic leukemia, eosinophilic leukemia/hypereosinophilic syndrome, chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocytopenia, and chronic myeloproliferative disease, unclassifiable. The classification likely is similar in dogs and cats, but the diagnoses are not always used consistently. No large case series for any of these disorders has been reported, although there are case reports for most of these diseases in dogs and cats.\(^9,10\) CML is extremely rare in domestic animals and is characterized by insidious onset of relatively non-specific clinical signs.

The CBC typically is characterized by marked increases in neutrophils or monocytes, but this depends on cell lineage of the neoplastic population. There may be marked neutrophilia with a disorderly left shift in chronic granulocytic leukemia, marked neutrophilia and monocytosis in chronic
myelomonocytic leukemia, and marked eosinophilia in eosinophilic leukemia. Mild non-regenerative anemia may be present. Marked inflammatory responses may be difficult to distinguish from CML involving neutrophils because both can be associated with similar clinical signs, marked neutrophilia with a left shift, marked granulocytic hyperplasia with disorderly maturation, < 30% blasts in the bone marrow, and infiltration of the liver and spleen with granulocytic precursors.

Diagnosis of CML often is by exclusion because consistent immunophenotypic and chromosomal markers have not yet been identified for dogs and cats with CML. Animals with CML have a longer survival time than those with AML, but most eventually develop a terminal blast cell crisis. Chronic myeloproliferative disorders are different from myelodysplastic syndromes, although both likely are clonal disorders. Myelodysplastic syndromes are characterized by peripheral cytopenias, normocellular or hypercellular bone marrow, < 30% blasts in the bone marrow, and prominent dysplastic changes in one or more hematopoietic lineages.

**Acute lymphoblastic leukemia (ALL)**

ALL is seen in young to middle aged dogs and in cats of variable age. Clinical findings in ALL include pale mucous membranes, splenomegaly, and hepatomegaly. Lymph nodes may be mildly to moderately enlarged. ALL typically is characterized by moderate to marked lymphocytosis involving immature lymphoid cells, moderate to marked non-regenerative anemia, neutrophilia, and thrombocytopenia. Immunophenotyping by flow cytometry may be helpful in the diagnosis of ALL. The neoplastic lymphocytes often express the cluster of differentiation (CD) antigen CD34. Cells of B lymphocyte lineage express CD20, CD21 and/or CD79a, whereas cells of T lymphocyte lineage express CD3 and either CD4 or CD8. In some reports, most dogs with ALL have neoplastic proliferation of B lymphocytes; whether B or T lineage is clinically relevant in dogs and cats with ALL is not clear. Most cats with ALL are infected with FeLV. The prognosis for dogs and cats with ALL is poor because of rapid progression and poor response to treatment. Remission with chemotherapy has been described, but usually is of short duration.

A relatively high percentage of dogs with lymphoma have low numbers of circulating neoplastic lymphocytes, based on detection of these cells by careful visual inspection of blood smears or by more sensitive DNA based test. In some dogs with lymphoma, there are numerous circulating neoplastic cells that may resemble the neoplastic lymphocytes in dogs with ALL. The distinction between circulating neoplastic cells from lymphoma and ALL may be important for prognosis and treatment. Dogs with multicentric lymphoma often have markedly enlarged lymph nodes, no other clinical signs of disease, and relatively normal CBC results, whereas dogs with ALL have only mildly to moderately enlarged lymph nodes, often are ill at time of presentation, and typically have peripheral cytopenias. Additional information from immunophenotyping may be helpful in distinguishing lymphoma with high numbers of circulating cells from ALL. The neoplastic cells from dogs with lymphoma typically do not express CD 34, whereas the neoplastic cells from dogs with ALL often express CD34. However, there may be overlap and distinction of dogs with ALL from dogs with lymphoma, bone marrow involvement, and circulating neoplastic lymphocytes can be difficult.

**Chronic lymphocytic leukemia (CLL)**

CLL is a disease of middle-aged to older dogs and cats of variable age. Clinical signs may be minimal and in many cases, the diagnosis is made incidentally from a CBC collected for routine health or presurgical evaluation. Total leukocytes often are very high, but in some cases are within normal
limits. There is a clonal population of neoplastic lymphocytes that often resemble well-differentiated lymphocytes based on routine microscopy, but cell size may be small, intermediate, or large. Nuclei may have smooth rather than condensed chromatin, and some cells may have cleaved nuclei. In some cases, the lymphocytes have a moderate amount of pale cytoplasm, compared to scant cytoplasm in normal lymphocytes. In most dogs with CLL, the proliferating neoplastic cells are large granular lymphocytes, which is a subset of T lymphocytes characterized by the presence of azurophilic granules in the cytoplasm. Non-regenerative anemia, if present, typically is mild. Neutropenia and thrombocytopenia are uncommon. The bone marrow and spleen may be infiltrated with neoplastic lymphocytes, but peripheral lymphadenopathy usually is absent. The clinical course for CLL may be months to several years. Some dogs with infectious diseases (e.g., *Ehrlichia canis* infection) have lymphocytosis that resembles CLL. Polymerase chain reaction for rearrangement of antigen receptors (PARR) may be helpful in differentiating polyclonal lymphocyte proliferations associated with infectious or inflammatory diseases from CLL.

REFERENCES


