Large Granular Lymphosarcoma/Leukemia in Dogs and Cats

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Definition and Description

Large granular lymphosarcaoma / leukemia is a neoplastic disease of lymphocytes that contain intracytoplasmic azurophilic granules. Large granular lymphocytes (LGL) can be found in the blood of healthy domestic species and usually constitute 10% or less of the total circulating lymphocyte pool.[2,7] Large granular lymphocytes have lymphocyte morphology, possessing a round or bean-shaped nucleus, and slightly basophilic cytoplasm. The major morphologic difference between LGLs and typical lymphocytes is that the former contain varying numbers (3 or more) of small to large azurophilic granules in their cytoplasm. Granular size usually is inversely proportional to the number of cytoplasmic granules.[5] In cats, the granules may be large with internal vesicles.[6] The exact origin of LGLs is unknown, however, studies have shown that at least two lines (cytotoxic T lymphocytes and natural killer cells) produce large granular lymphocytes. Studies show that most large granular lymphocytes in dogs are of T cell origin, with the minority of natural killer (NK) cell origin.[2,9] Most cases of LGL leukemia originate outside of the bone marrow and thus are technically lymphosarcoma. Infiltration of the bone marrow subsequently can occur, and patients will present with a leukemic blood picture.[2]

Etiology

The etiology of LGL leukemia/lymhphosarcoma currently is unknown. One study demonstrated that LGL cells produced retroviral particles suggestive of C oncoviruses (such as FeLV) and Spumaviruses[1], implying a potential

underlying viral component.

Gender Predilection

A clear gender predilection does not occur in cat. In contrast, several studies in dogs have found a significant bias with females more likely to present with LGL neoplasms. The male to female sex ratios were 1:7-8.[2,9]

Clinical Presentation

Clinical signs of disease may differ among individuals and depends on sites of tumor infiltration. In dogs, the condition is primarily of splenic origin. Affected individuals may be asymptomatic with large granular lymphocytes in circulation, or may have an indolent condition with periods of lethargy or an aggressive malignancy.[2,7] Common nonspecific clinical signs in dogs include lethargy, depression, and anorexia. Other clinical signs may include dyspnea, nonproductive cough, polydypsia, enlarged lymph nodes, jaundice, and hepatosplenomegaly. Laboratory findings include anemia, neutropenia, and thrombocytopenia.[2] Periodic arthritic pain and intermittent effusion were present in one patient.[1] Cutaneous and gastrointestinal (GI) associated lymphoma also have been noted in dogs.[2]

Diagnosis of LGL neoplasia is based on clinical signs in cats and disease diagnosis is equally as difficult. There is a predilection for infiltrates or tumor formation in specific organs in cats. These sites of origin, listed in decreasing frequency, are mesenteric lymph nodes, small intestine, pancreatic-duodenal lymph node, spleen, pancreas, liver, kidney, stomach, lung, myocardium, mediastinum, salivary glands, and thyroid gland.[5] In cats, LGL lymphomas will develop within the mucosa of the small intestine and may extend into the ileal wall.[4,8] Common clinical signs associated with feline LGL lymphoma include vomiting, anorexia, diarrhea, and weight loss.[4] Perforation of the GI wall may occur giving rise to melena or hematochezia.[4] Palpation, ultrasound, or endoscopy may reveal splenomegaly, thickening of the small intestinal wall, enlarged mesenteric lymph nodes, and ascites. If hepatic involvement is present, jaundice may occur.[4]

Laboratory Diagnosis

Marked lymphocytosis of large granular lymphocytes has been reported with chronic *Erlichia canis* infection, and mild LGL lymphocytosis can occur with any inflammatory process. Infections, particularly rickettsial infection, must therefore be excluded before a diagnosis of LGL leukemia/lymphosarcoma can be made.[2] LGL neoplasms are best diagnosed via light microscopy by examining Wright-stained blood smears and fine-needle aspirates of spleen and lymph node. Wright staining of LGLs will reveal lymphocytes with large granules that are magenta to purple and may have an achromic area surrounding the azurophilic core (Figs. 1 and 2). LGL lymphomas should be separated from other lymphomas that are agranular because LGL lymphomas are more refractory to treatment. Hematoxylin and eosin stain has been

unsatisfactory in demonstrating the granules in histologic sections. This may make diagnosis of LGL lymphoproliferative diseases more difficult. Other methods of diagnosis are available in some diagnostic laboratories and academic institutions that involve immunohistochemistry and detection of specific CD proteins. However, immunophenotype apparently does not correlate with clinical signs, especially in dogs.[2] CD proteins will identify the various LGL subtypes such as $CD3^-$ or NK cells and $CD3^+$ (T) cells. Other cell markers have been used to identify the cellular lineages. The most common phenotype of LGL leukmias/lymphosarcomas in cats are $CD4^-$, $CD8^+$, $CD56^+$, $CD57^-$, which indicate a T cell origin. LGL lymphosarcomas of intestinal origin are characterized by a $CD103^+$ phenotype.[5] The most common form of LGL neoplasia in dogs is T-cell lymphoma that is $CD4^-$ and $CD8^+$.[1] However, further CD protein analysis does not appear useful. Markers are variable in tumors of both origins and may change in the same cell line with time, even to the point of appearing myeloid based on immunophenotype.[5,9] Another method of analysis is to use the polymerase chain reaction (PCR) to determine that all LGLs are of the same genetic lineage (monoclonality). While suggestive of neoplasia, clonality does not prove or imply malignancy.[9]

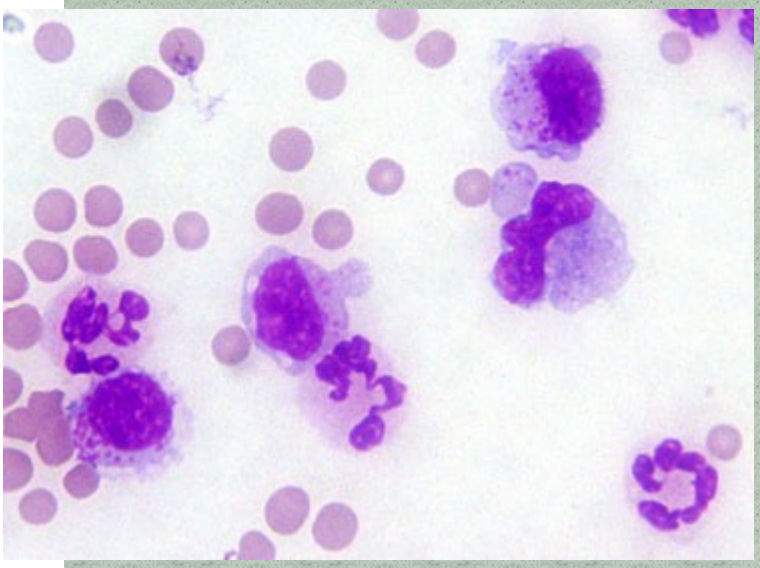

Figure 1. Three large granular lymphocytes with azurophilic cytoplasmic granules in the blood of a cat. Three neutrophils and a monocyte also are present (Wright stain).

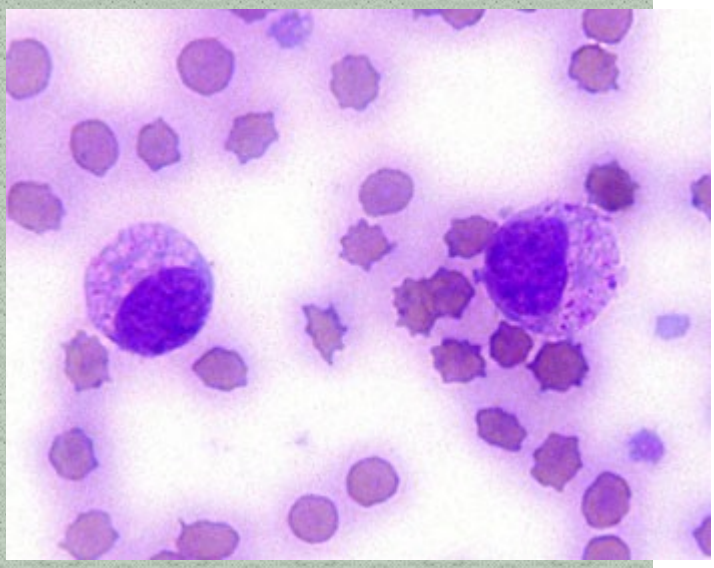

Figure 2. Closer view of two large granular lymphocytes in the blood of a dog. Achromic areas surround the azurophilic granule core (Wright stain).

Hematologic and Biochemical Abnormalities

Common findings in the complete blood count report are large granular lymphocytes that comprise greater than 10% of the total circulating lymphocytes for 3 or more months (Figs. 1 and 2). The presence of a negative titer to *Erlichia* spp. excludes a possible cause of nonneoplastic proliferation of large granular lymphocytes.[2] Fine-needle aspirates of the spleen, liver, and lymph nodes may reveal infiltrates of large granular lymphocytes (Fig. 3). Bone marrow aspirates may or may not be hypercellular and contain similar cells.

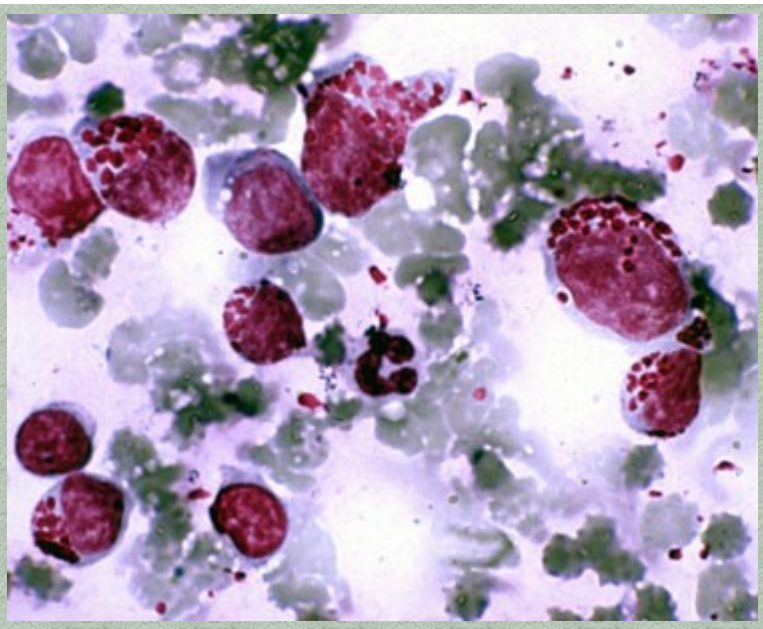

Figure 3. Fine-needle aspirate from the lymph node of a cat with large granular lymphoma. Notice the large, magenta to purple, cytoplasmic granules (Wright stain).

Increased hepatic enzyme activities and creatinine concentration, as well as other blood chemistry abnormalities, may be present depending on the severity of disease and the organs affected. However, biochemical profile data also may be within the reference intervals.

Cats with suspected LGL neoplasias also should be tested for FeLV.

Gross Lesions and Histopathology

Findings on post mortem relate to sites of infiltration by the tumor. The most common gross findings in LGL neoplasia include splenomegaly, mesenteric lymphadenopathy, and thickening of the small intestinal mucosa. Histologically, leukemic infiltrates are present in various tissues.[2,4] Cytoplasmic granules may be difficult to discern in neoplastic lymphocytes on hematoxylin and eosin-stained tissue sections. Immunohistochemistry may be helpful in identifying the cell types present (see CD markers in "Laboratory Diagnosis" above).

Radiographic and Ultrasonographic Imaging

Survey radiographs of the thorax and abdomen may reveal soft tissue masses and enlarged lymph nodes. Ultrasound also can be used to detect enlargement of the kidneys, lymph nodes, liver, and spleen.

Treatment and Follow-up

Prednisone and chlorambucil are effective in treating LGL neoplasms in dogs. However, standard combination chemotherapy protocols for lymphoma also may be tried. One study showed that longevity could be greater than three years with prednisone and chlorambucil administration alone. Studies have also demonstrated that the immunophenotype does not correspond to the clinical prognosis.[2]

In cats, treatment regimens have not met with great success. Treatments used have been standard combination chemotherapy protocols for lymphoma (vincristine, cyclophosphamide, methotrexate, L-asparginase, and prednisone).[3] None of the published clinical studies have mean survival times greater than a few months with any treatment regimen.[3]

Patients should be monitored weekly with complete blood count and physical examination. Patients that are asymptomatic can become symptomatic with little warning.

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