Hematopoietic Tumors of Cats

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The feline leukemia virus (FeLV) causes the majority of both lymphoid and myeloid tumors in pet cats. Collectively these tumors account for approximately one-third of all feline tumors and are a major cause of death in the cat population. The most common FeLV-induced tumor is lymphosarcoma which is classified into multicentric, thymic, alimentary and unclassified forms depending on the location of the major gross lesions. Although 30% of cats with lymphosarcoma have been found to be negative for FeLV in tests for the virus, immunological and epidemiological evidence has shown that FeLV causes all lymphosarcomas irrespective of whether or not they produce infectious virus. Since FeLV is an infectious agent, the development of lymphosarcoma and the FeLV-induced myeloid tumors can be prevented by means of a simple "test and removal" program in which FeLV infected cats are permanently separated from uninfected cats.

Introduction

Most red and white blood cells must be made outside the blood stream and delivered into it, at the same rate as they leave it or die. Hematopoietic tissue is a form of connective tissue that is specialized to produce blood cells and to remove old blood cells from the circulation. Within hematopoietic tissue, further specialization has occurred resulting in myeloid tissue that produces erythrocytes, granular leukocytes (neutrophils, eosinophils and basophils), monocytes and platelets, and lymphatic tissue that produces most of the nongranulated leukocytes (lymphocytes). Myeloid tissue which produces blood cells and filters blood is confined to the marrow cavities of bones. Lymphoid tissue also produces blood cells and filters tissue fluid, lymph and blood. Lymphatic tissue is highly specialized for the production of plasma cells; the cells that are primarily concerned with making antibodies. However, not all plasma cells are produced in lymphoid tissues, some are produced in loose connective tissue and in myeloid tissue. The cells of lymphatic tissue lie in a network of reticular fibers. Lymphatic structures that are designed to filter tissue fluid are usually located under wet epithelial surfaces, are not encapsulated and prevent invading organisms from gaining entry into the body. Tonsils and Peyer's patches are examples of lymphatic structures, that filter tissue fluid. Lymphatic structures that filter lymph and blood are the lymph nodes and spleen respectively.

Incidence of Hematopoietic Tumors

Primary hematopoietic tumors can be either myeloid or lymphoid. Hematopoietic tumors occur frequently in many animal species, usually in young animals, indicating that infectious agents cause these tumors. Approximately one-third of all cat tumors are hematopoietic tumors, and the majority of these (90%) are lymphoid tumors (lymphosarcoma).[1] Thus, as a group, these tumors are the most common primary feline tumors.

Tumors metastatic to the hematopoietic system are also common. Mammary carcinomas, oral tumors and various other feline tumors often metastasize to the lymph nodes and spleen. Most tumors that metastatize to the hematopoietic system do so to the lymphoid rather than to the myeloid compartment.

Etiology

In contrast to most tumors, hematopoietic tumors often occur in young animals indicating that infectious agents cause these tumors. RNA tumor viruses, which are now classified within the Retrovirus (reverse transcriptase containing virus) family, cause naturally occurring hematopoietic tumors in northern pike, chickens, mice, hamsters, guinea pigs, cats, cows, sheep, and apes.[2] In 1964 Professor William Jarrett and his colleagues discovered the feline leukemia virus (FeLV) in a cat with lymphosarcoma. FeLV is now known to be the cause for almost all of the hematopoietic tumors of cats.[3,4] For more information concerning other FeLV diseases refer to the papers on the Feline Leukemia Virus, Feline Leukemia Virus Non-Neoplastic Diseases and the Feline Sarcoma Virus in this issue.

Lymphoid Tumors

There are three types of lymphoid tumors of cats. They are: 1) lymphosarcoma, 2) plasma cell myeloma, and 3) thymomas. Lymphosarcoma is a neoplastic disease of lymphocytes; plasma cell myeloma is a neoplastic disease of plasma cells; and thymoma is a neoplastic disease of the thymic epithelial cells.

Lymphosarcoma

Incidence

The cat has the highest incidence of lymphosarcoma (LSA) of any animal and LSA accounts for 90% of all feline hematopoietic tumors.[1] Clinically, LSA and reticulum cell sarcoma are the same disease. These diseases occur annually in about 200 cats per 100,000 cats in the population.[5] No one breed, or sex of cat, is more susceptible to LSA than any other.[6] Since the disease is the result of FeLV infection and transformation of lymphocytes, any susceptible cat that is infected by the virus may develop the disease. Random bred domestic short or long haired pet cats, however, develop LSA later in life, on average, than pedigree cats, probably because pedigree cats are bred and live in catteries and are thus crowded with other cats earlier in

their lives than domestic cats and are therefore more apt to be infected with FeLV and develop LSA at a younger age.[6] The average age of LSA occurrence is three years for FeLV positive cats but is seven years for FeLV negative cats with LSA.[2,7] Most feline LSAs are of T cell origin but B cell LSAs occur in the alimentary form of the disease.[2]

Seventy-percent of cats with LSA are FeLV positive [Figure 1A] whereas 30% have no detectable FeLV antigens nor infectious FeLV in any tissues [Figure 1B], including their LSA cells [Table 1].[2,7-11]

Table 1

Occurrence of FeLV in Pet Cats with Lymphosarcoma

Form of Lymphosarcoma	Number of Cats Tested	Number FeLV Positive	Percent FeLV Positive	Percent FeLV Negative
Multicentric	198	159	80.3%	19.7%
Thymic	174	134	77.0%	23.0%
Alimentary	69	16	23.2%	76.8%
Unclassified	13	5	38.5%	61.5%
	454	314	69.0%	31.0%
Form unknown	53	46	86.8%	13.2%
Totals	507	360	71.0%	29.0%

Cats with FeLV negative LSA are two to three times older than cats with FeLV positive LSA [Figure 2].[2,11,12] However, both FeLV positive and FeLV negative (nonproducer) LSA cells have the tumor-specific feline oncornavirus associated cell membrane antigen (FOCMA) on their membranes, [Figure 3] indicating that FeLV causes both types of feline LSA.[2,7,9-11] The occurrence of FeLV in cats with LSA varies according to the form of the disease [Table 1],[2] the classification of which is based on the anatomical distribution of the major tumor lesions.[13] The four forms of feline LSA occur at different frequencies in different parts of the world,[2,14,15] for example, multicentric LSA is most common in New York[2] while alimentary LSA occurs most frequently in Scotland,[14] and leukemia occurs most often in Boston.[15] The reasons for the geographic differences in the occurrence of LSA at different anatomical sites are not known but may be due to the occurrence of different substrains of FeLV in different areas, to the different genetic composition of pet cats in the U.S. and Scotland, or to different criteria used to classify LSA cases.
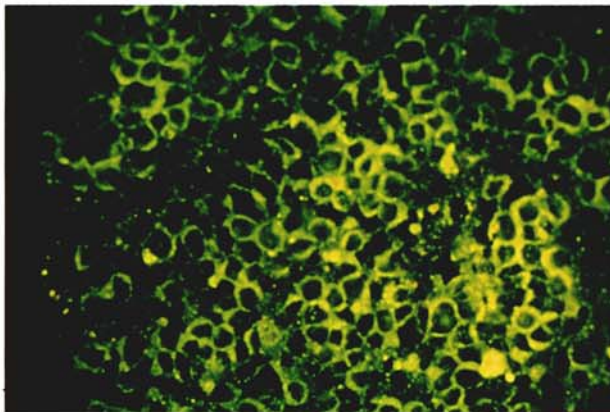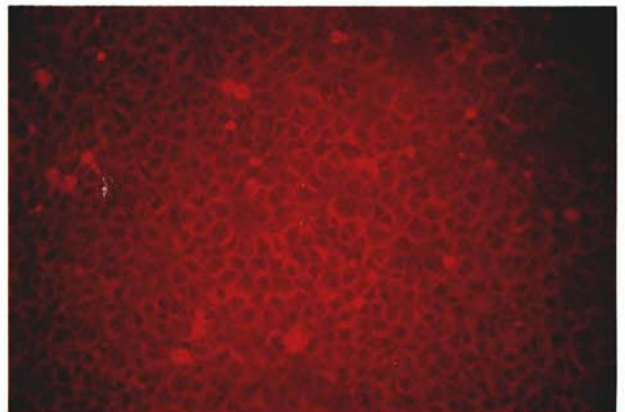
Figure 1A

Figure 1B

Figure 1— Examination of a tumor imprint of feline lymphosarcoma cells for FeLV by the immunofluorescent antibody test. (A) Strong cytoplasmic fluorescence indicates presence of FeLV antigens and replicating FeLV. (B) Absence of cytoplasmic fluorescence (counterstained red) indicates lack of FeLV antigens and lack of replicating FeLV in these FeLV negative lymphosarcoma cells.
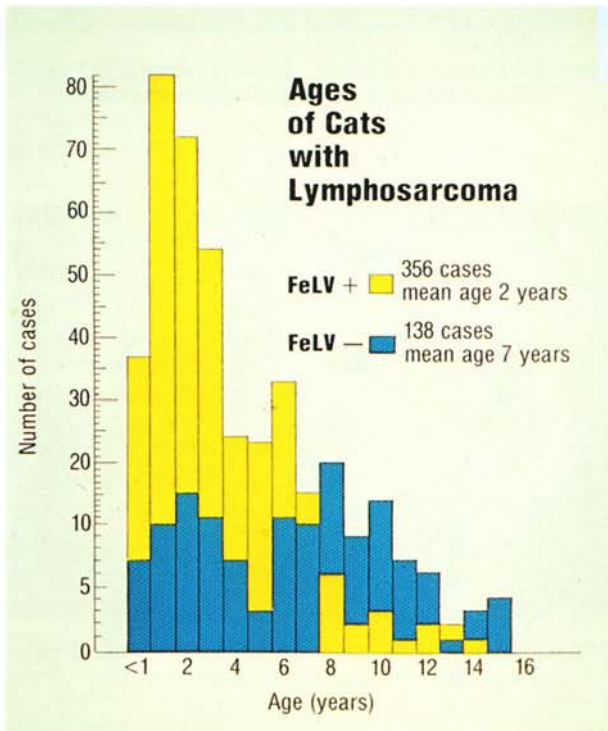
Figure 2 (Left)— Ages of 494 cats with lymphosarcoma. FeLV positive cats are indicated by the yellow bars and FeLV negative cats are indicated by the blue bars.

Figure 3 (Below)— Positive immunofluorescent reaction showing the tumor-specific feline oncornavirus-associated cell membrane antigen (FOCMA) on the cell membranes of feline lymphosarcoma cells.
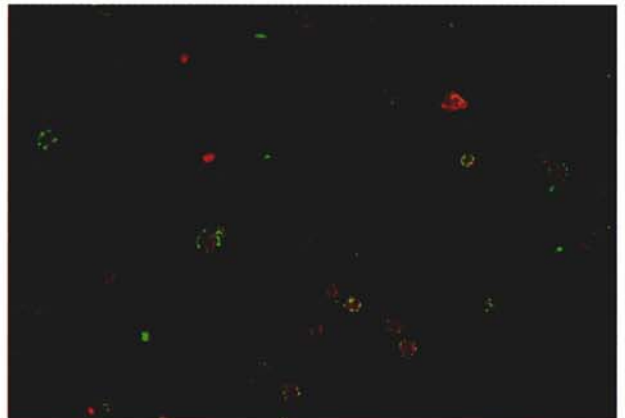
The Four Forms of Feline Lymphosarcoma

Multicentric LSA: This form of LSA was observed most commonly in a study of pet cats that my laboratory conducted,[2] occurring in 198 of the 454 (43.6%) cats in which the form of LSA was known [Table 1]. However, multicentric LSA was the second most common form of LSA of cats in Scotland.[14] In this form of the disease the tumor may be located in the lymph nodes, spleen, liver and kidneys, either alone or in any combination of these sites [Figures 4-7]. The average age of cats with multicentric LSA is four years and 80% are FeLV positive [Table 1].[2] The clinical signs are varia-

Figure 4— Multicentric lymphosarcoma — enlarged sub-
mandibular lymph nodes.

Figure 5— Multicentric lymphosarcoma — enlarged nodu-
lar spleen infiltrated with lymphosarcoma cells.
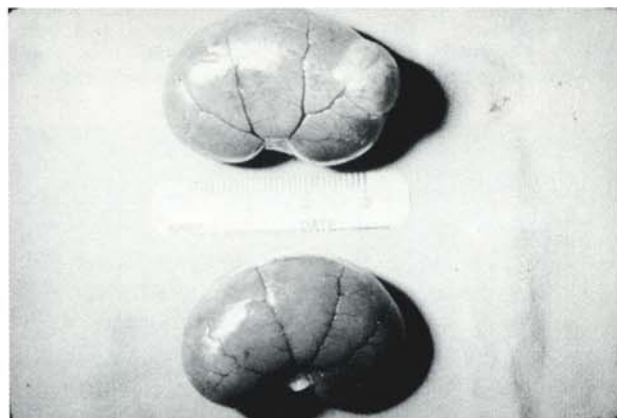
Figure 6— Multicentric lymphosarcoma — a small nodule of
lymphosarcoma can be seen in one kidney.
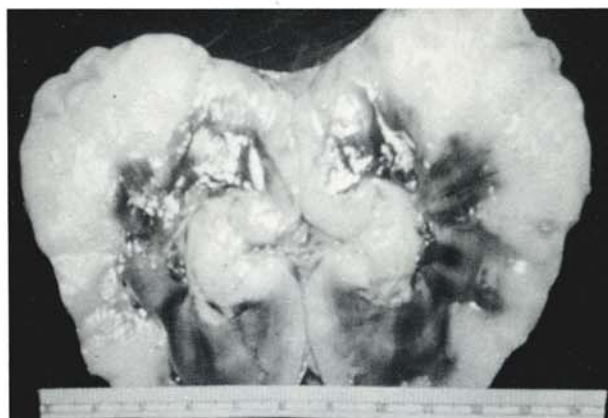
Figure 7— Multicentric lymphosarcoma — a kidney mas-
sively infiltrated with lymphosarcoma cells.

ble and depend on the location of the tumor.[6] Cats
may be polyuric and polydipsic indicating renal
LSA or may be icteric due to LSA involving the liver.
Many of these cats are anemic, the anemia being
the nonregenerative normocytic normochromic
type.[6,16] I classify most cats with leukemic blood
profiles as having multicentric LSA unless they
have obvious thymic or alimentary LSA along with
the leukemic blood profile [Figures 8, 9].

Thymic LSA: This was the second most com-
mon form of LSA in our study occurring in 174 of
the 454 (38.3%) cats [Table 1].[2] In this form of LSA the
tumor arises from the T-lymphocytes of the
thymus, but lymphoid masses can occur through-
out the chest cavity and can encircle the heart [Fig-
ure 10].[2,17] The tumor may grow to a very large size
before the cat shows any clinical signs. Hy-
drothorax is usually present causing partial col-

Figure 8— Multicentric lymphosarcoma — the bone marrow is infiltrated with lymphosarcoma cells.

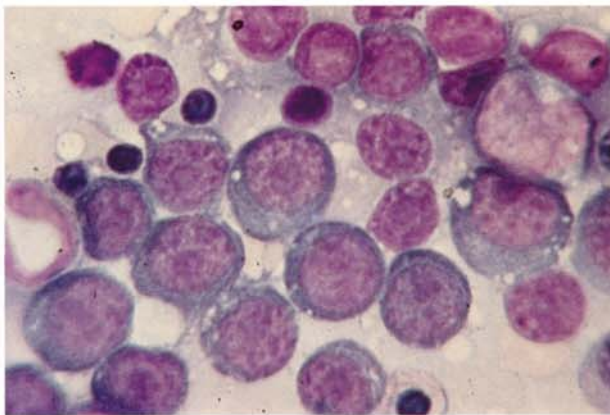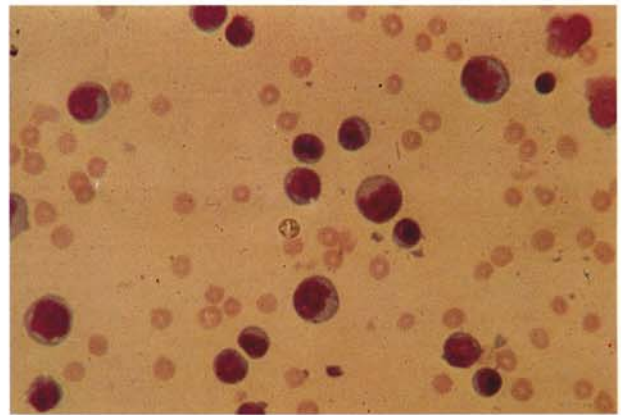Figure 9— Multicentric lymphosarcoma — FeLV positive peripheral blood with lymphoblasts and lymphocytes. This cat has multicentric lymphosarcoma with a leukemic blood profile. Some hematologists consider this condition to be lymphoblastic leukemia.
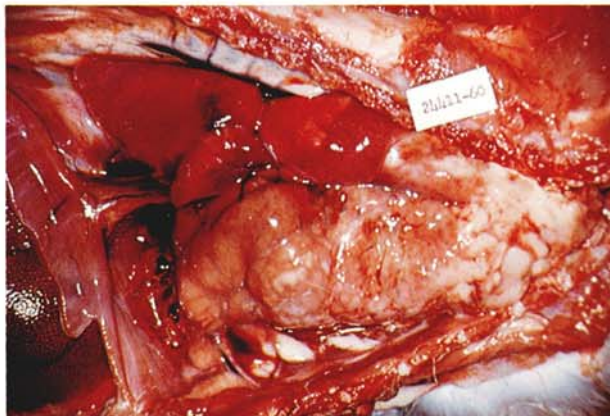

Figure 10— Thymic lymphosarcoma — an FeLV positive large thymic lymphosarcoma mass occupies the chest cavity and completely encases the heart.

Table 2

Occurrence of FeLV in Alimentary Lymphosarcoma

Site	Number Tested	Percent FeLV Positive	Percent FeLV Negative
Intestine	41	4.9%	95.1%
Stomach	11	9.1%	90.9%
Mesenteric lymph nodes	17	76.4%	23.6%
	69	23.2%	76.8%

lapse of the lungs resulting in respiratory difficulty. Thus, tachypnea, intolerance to exercise, and muffled heart sounds on auscultation are clinically evident. In addition, the chest wall is noncompressible when palpated at the thoracic inlet due to the thymic mass, in contrast to the very easily compressible chest of a normal cat. Seventy-seven percent of cats with this form of LSA are FeLV positive and are younger (average age 2.5 years) than cats with the other forms of LSA [Table 1].[2]

Alimentary LSA: Alimentary LSA was the third most common form of the disease in our study, occurring in 69 of the 454 (15.2%) cats [Table 1].[2] In contrast, alimentary LSA was the most common form observed in cats in Scotland.[13] In this form of the disease the tumor localizes at any site in the gastrointestinal tract from the stomach to the colon, and/or in the mesenteric lymph nodes [Figures 11-14]. The kidneys may also be involved but tumor development in other organs is unusual. Most of the LSAs that localize solely in the alimentary tract are B cell tumors arising from B lymphocytes in the lamina propria. The average age of cats with alimentary LSA is much higher, eight years, than that of cats with the other forms of LSA.[2,12] The occurrence of FeLV negative LSA in cats with the alimentary form of the disease, especially with tumor localization solely in the gastrointestinal tract is higher, 76.8% , than among LSA cats in general [Tables 1, 2]. Cats with alimentary LSA usually have

Figure 11— Alimentary lymphosarcoma — an FeLV negative gastric lymphosarcoma mass protruding from the stomach wall.

Figure 12— Alimentary lymphosarcoma — an FeLV negative intestinal lymphosarcoma mass in the small intestine (ileum).

Figure 13— Alimentary lymphosarcoma — an FeLV negative intestinal lymphosarcoma mass in the large intestine.
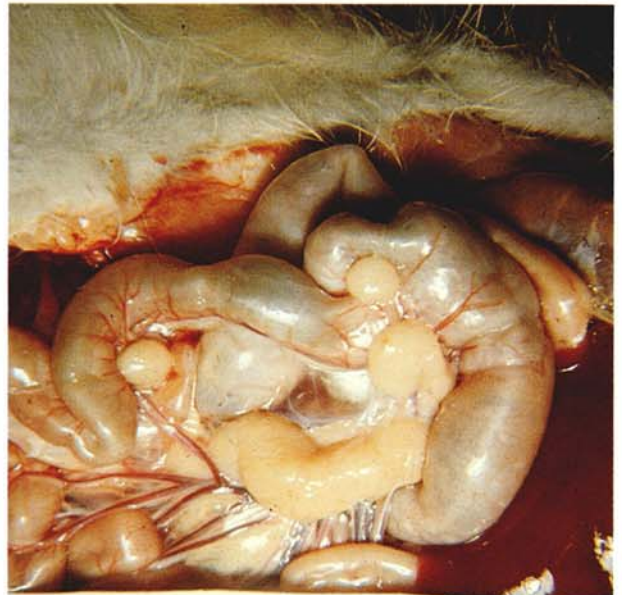
Figure 14— Alimentary lymphosarcoma — enlarged mesenteric lymph nodes in an FeLV positive cat. There were no lymphosarcoma lesions in the gastrointestinal tract of this cat.

palpable tumors in the abdomen and may exhibit vomiting, diarrhea or constipation and weight loss. Anemia is rare in cats with alimentary LSA, probably because most of these cats are FeLV negative. This observation supports the concept that FeLV, rather than the LSA, is responsible for the anemias seen in many cats with the other three forms of LSA, which are more often FeLV positive.

Unclassified LSA: This was the least common form of LSA observed in cats in our study, occurring in only 13 of the 454 (2.9%) cats [Tables 1, 3].[2] In this form of LSA the lesions may be located in the eye or

Table 3

Occurrence of FeLV in
Unclassified Lymphosarcoma

Site	Number Tested	Percent FeLV Positive	Percent FeLV Negative
Skin	8	12.5%	87.5%
Eye	3	100%	0%
CNS	1	100%	0%
Nasal cavity	1	0%	100%
	13		

Figure 15— Unclassified lymphosarcoma — lymphosar-coma cells infiltrating the iris and anterior chamber of the eye of an FeLV positive cat with ocular lymphosarcoma.

Figure 16— Unclassified lymphosarcoma — lymphosar-coma mass behind the orbit causing enlargement of the eye in an FeLV positive cat with ocular lymphosarcoma.

Figure 17— Unclassified lymphosarcoma — discrete, raised masses in an FeLV negative cat with skin lymphosarcoma.

Figure 18— Unclassified lymphosarcoma — hind leg paral-ysis caused by a lymphosarcoma mass which infiltrated the spinal canal and compressed the spinal cord.

Figure 19 (Right)— Unclassified lymphosarcoma — a large nasal lymphosarcoma mass in an FeLV negative cat.

skin or central nervous system and/or in other nonlymphoid tissues [Figures 15-19]. LSA of the skin is usually an FeLV negative tumor and, since skin LSA is the most common site of unclassified LSAs, cats with unclassified LSA have a higher over-all occurrence of FeLV negative tumors than do cats with LSA in general. Cats with unclassified LSA are older (average age 8.6 years) than most cats with the other forms of LSA.

FeLV Negative Lymphosarcomas

An effective immune response to FeLV does not always guarantee that a cat will be protected from the development of LSA simply as a result of its immunity to FeLV infection. During local lymphoid infection, the FeLV genome may become integrated into the chromosomes of a small number of lymphoblasts before the immune system responds effectively. Even though the cat may produce FeLV neutralizing antibody and reject the virus (but not produce LSA protective FOCMA antibody) the FeLV genome may still be able to transform the "infected" lymphoblast into a lymphosarcoma cell even without stable genome integration or the production of any FeLV antigens or infectious FeLV. Thus, some transiently infected pet cats develop LSA but do not replicate or shed any FeLV.[7-9] Both FeLV positive and negative LSA cells express the tumor-specific antigen FOCMA on their cell membranes.[7,9] We have recently found an epidemiologic association between exposure to FeLV and the development of FeLV negative LSA similar to that which exists between FeLV exposure and the development of FeLV positive LSA.[4,7] We have observed 1612 pet cats for the occurrence of LSA. Of these cats, 1074 cats were controls who had never been exposed to FeLV, while 528 cats were exposed to FeLV infected cats under natural conditions in their households. The exposed group of cats consisted of 389 uninfected cats and 149 persistently viremic cats. None of the 1074 unexposed uninfected cats developed FeLV negative LSAs but 11 of the 389 exposed uninfected cats developed FeLV negative LSAs and 33 of the 149 infected cats developed FeLV positive LSA. The difference in LSA occurrence between the uninfected unexposed and uninfected exposed cats is statistically significant at less than $p=0.001$ by the Chi square test. Our findings indicate that FeLV causes both the FeLV positive and negative LSAs of pet cats.

Hematologic Values in Cats with Lymphosarcoma

Leukemic Blood Profile

In some cats, neoplastic lymphocytes may be present only in the blood and bone marrow, a condition which is referred to as leukemia in humans.[6,15,16,19] However, it is more common to find a leukemic blood profile in cats with lymphosarcoma where the neoplastic lymphocytes escape from the solid lymphoid tumor mass and enter the blood.[6,16] In our studies, leukemia involving only the blood and bone marrow without concurrent lymphoid tissue neoplasia (LSA) was rare. However, we found that 27% of cats with LSA had leukemic blood profiles in addition to their solid tissue LSA. In contrast to our observation, Cotter and Essex found that leukemia involving only the blood and bone marrow occurred more frequently in cats in Boston.[15] The majority of cats with leukemic blood profiles that we have studied had FeLV positive LSA (17 out of 20 cats), and only three of the 23 cats with FeLV negative LSA had a leukemic blood profile. Most of the FeLV positive LSA cats with leukemic blood profiles, eight of 17 cats (47%), had decreased total WBC counts, but normal WBC counts were found in three of the 17 cats (18%) and elevated WBC counts were found in six of the 17 cats (35%).

Some veterinary pathologists, and I, feel that leukemia is simply a manifestation of LSA in which the neoplastic lymphocytes are found in the blood.[20] The bone marrow can be considered to be a lymphoid organ since a few lymphocytes are produced there in normal cats. I, therefore, feel that leukemia involving only the blood and bone marrow, without concurrent tissue LSA, is a manifestation of LSA and should be classified as multicentric LSA [Figures 8, 9]. However, cats with multicentric, thymic, alimentary or unclassified LSA may have concurrent leukemic blood profiles. I classify these cats according to their major form of LSA, for example, thymic LSA with a leukemic blood profile. When leukemia cells fill the bone marrow they can destroy the normal cells causing anemia as the result of erythroid cell destruction, or thrombocytopenia and bleeding tendencies if the megakaryocytes are destroyed. Since leukemia cells spread mainly via the blood, they can infiltrate the spleen and liver causing marked enlargement of these organs.

Bone Marrow Changes in Cats with LSA

In many cats with LSA the maturation and numbers of erythrocytes and granulocytic leukocytes are altered. Usually the alterations are due to the effect of FeLV on the bone marrow cells and are not caused by LSA cells invading the bone marrow. Our observation that cats with FeLV negative LSA usually have normal hemograms (see data below) supports the hypothesis that FeLV directly induces hematological changes by its effect on the bone marrow cells.

Erythroid Changes in Cats with LSA

Thirty-four out of the 50 cats (68%) with FeLV positive LSA that we have studied hematologically were anemic [Table 4].[21] Seven of these 34 cats (21%) had mild anemias (PCV between 20% to 25%)

Table 4

Anemia Concurrent with Feline Lymphosarcoma

FeLV Status	Number of Cats Tested	Packed Cell Volume: Normal	20-25%	Below 20%
Positive	50	16 (32%)	7 (14%)	27 (54%)
Negative	23	21 (91.4%)	1 (4.3%)	1 (4.3%)
	73	37 (50.7%)	8 (10.9%)	28 (38.4%)

whereas 27 (79%) of the 34 cats had severe anemias (PCV below 20%). In contrast, only two out of the 23 cats with FeLV negative LSA that we studied were anemic—one of these cats had a mild anemia and the other had a severe anemia. Thus, while 68% of the FeLV infected LSA cats were anemic, 91% of the FeLV negative LSA cats were not anemic. Most FeLV positive cats with LSA had a secondary nonregenerative normocytic normochromic anemia concurrent with their LSA. There was little or no evidence of RBC regeneration in these cats since their reticulocyte counts were normal or low despite the severe anemias. A few cats had a regenerative anemia with increased reticulocyte counts, but it is possible that this form of anemia was simply the initial effect of FeLV and that these cats would have ultimately developed a nonregenerative anemia. Mackay and coworkers have reported similar observations to those described above.[22] They found that 18 out of the 33 (55%) pet cats with naturally occurring LSA had concurrent anemias and that 16 of

these 18 (89%) cats had normocytic normochromic nonregenerative anemias. Only two cats had increased reticulocyte numbers indicating regenerative anemias.

Granulocytic Leukocyte Changes in Cats with LSA

In our survey of the occurrence of a leukemic blood profile in cats with LSA we found that 53 of the 73 (72.6%) cats did not have a leukemic blood profile [Table 5].[21] Of these 53 cats, 33 (62%) had FeLV positive LSA and 20 (38%) had FeLV negative LSA. Most, 17 of the 33 (52%) FeLV positive cats with LSA had a normal WBC count, 12 cats (36%) had a decreased WBC count, and only four cats (12%) had an elevated WBC count. Similarly, 11 of the 20 (55%) cats with FeLV negative LSA had a normal WBC count, eight of the 20 cats (40%) had an elevated WBC count and only one cat (5%) had a decreased WBC count.

Thus, unlike humans with lymphoid tumors, most cats with lymphoid tumors do not have leukemic blood profiles or an elevation in their total numbers of leukocytes. Anemias often occur as a preleukemic syndrome in both humans and cats, although in cats primary FeLV-induced anemias are far more common than pure red cell aplasia of humans.[23]

Biological Behavior of Untreated Lymphosarcoma

In general, cats do not exhibit signs of any disease until that disease is quite advanced. Thus, cats with any of the four forms of LSA are usually presented to the veterinarian at an advanced stage of the disease. Cats with FeLV positive LSAs are usually anemic and, without supportive care and antitumor treatment, will usually die within two to four

Table 5

Leukocyte Alterations with Feline Lymphosarcoma

FeLV Status	Number Tested	Non-Leukemic Profile Normal 8-18,000*	Elevated Above 18,000	Decreased Below 8,000	Leukemic Blood Profile Normal 8-18,000	Elevated Above 18,000	Decreased Below 8,000
Positive	50	17 (34%)	4 (8%)	12 (24%)	3 (6%)	6 (12%)	8 (16%)
						34%	
Negative	23	11 (47.8%)	8 (34.8%)	1 (4.3%)	1 (4.35%)	1 (4.35%)	1 (4.35%)
						13.1%	

*/mm³

weeks. Cats with FeLV negative LSAs are usually not anemic and, untreated, will live longer than those cats with FeLV positive LSAs.

Biologically Active Tumor Cell Products

Various humoral factors are produced by normal lymphocytes which stimulate or depress activities of other lymphocytes and other leukocytes. However, very little is known about the production of any biologically active tumor cell products by feline LSA cells. Alterations in the gamma globulin concentration in the plasma of cats with LSA have been observed but the frequency of these changes has not been well documented. We have found that several cats with LSA have had polyclonal elevations of their serum gamma globulin that were probably a result of lymphoid stimulation and not a unique product of the tumor cells. In a recent study it was reported that a factor(s) was present in the serum of a cat with T cell skin LSA which stimulated autologous tumor cells, but not normal lymphocytes.[24]

Metastases

Lymphosarcoma of cats is probably a clonal neoplasm, that is, derived from the growth of a single neoplastic lymphocyte. Thus, the widespread anatomical distribution of LSA lesions represents widespread metastases of the neoplastic lymphocytes via the lymphatic pathways.

Diagnostic Methods

Diagnosing feline LSA can be easy in some cases and difficult in others. A general history of multiple cat ownership or exposure to other cats should be sought for any sick cat since FeLV-induced diseases such as LSA occur as a result of contagious spread of the virus.[25] The veterinarian should inquire as to whether other cats in the owner's household have died recently and if so determine the cause of death. A complete physical examination must include careful palpation of all peripheral lymph nodes, all abdominal organs, and examination of the thorax by compressing the ribs at the anterior aspect of the thorax to determine if a space occupying thymic LSA mass is present. The mucous membranes should be examined for evidence of anemia or icterus. The clinical findings in cats with LSA are often variable and multiple [Table 6]. If a mass is palpated in the chest, as determined by the lack of compressibility of the chest wall, then a thoracic radiograph or thorocentesis and cytology should be performed.

The only procedures that will enable a diagnosis of LSA to be made are cytological or histo-

Table 6

Clinical Findings in Cats with Lymphosarcoma

Clinical Finding*	Percent of Cases Finding Observed
Pale membranes	60%
Abdominal mass	37%
Hydrothorax	28%
Peripheral lymphadenopathy	19%
Pyrexia	16%
Enlarged kidneys	16%
Cachexia	12%
Icterus	7%
Splenomegaly	6%

*Most cats with LSA have more than one of the above clinical findings.

pathological evidence of neoplastic lymphocytes (see paper on cytologic procedures of tumors in this issue). A lymph node biopsy consisting of removal of the entire node rather than a needle aspiration is recommended. Bone marrow aspiration and cytology can be diagnostically helpful in about 15% to 20% of the cases where neoplastic lymphoblasts are present in the bone marrow. Careful morphological evaluation of peripheral blood lymphocytes can also be very helpful in diagnosing LSA with a leukemic blood profile although only 20% to 25% of LSA cats are overtly leukemic.[26] An FeLV test, whether positive or negative is not diagnostic for any feline disease, including LSA.[27]

Pathologic Findings

The pathologic diagnosis of LSA is not always simple. Neither enlargement of lymphoid structures nor, microscopically, the presence of primitive or immature lymphoid cells is diagnostic of LSA. Since malignant lymphoid cells are morphologically indistinguishable from normal lymphoid cells and LSA must be differentiated from reactive lymphoid hyperplasia. The persistence of any of the architectural components of normal lymph nodes and a variety, rather than a uniformity, of cell types argues for hyperplasia.[28] In contrast, the obliteration of normal lymphoid architecture, the uniformity of large cells, large numbers of mitotic figures and the presence of highly undifferentiated cells support the diagnosis of LSA. Neoplastic lymphoid cell invasion of such nonlymphoid organs as the heart, stomach, kidney or liver is a sure

indication of LSA. It is possible, in the research laboratory, to determine immunologically, if lymphoid cells are malignant by the detection of FOCMA on their cell membranes (see the feline leukemia virus paper in this issue) [Figure 3].[9,10] However, since viable cells are required for this test it is impractical for routine use by veterinarians.

There are four histogenic cell types of lymphosarcoma: 1) poorly differentiated stem cell LSA, 2) lymphoblastic LSA, 3) lymphocytic and prolymphocytic and 4) histiocytic, histioblastic and histiolymphocytic (formerly called reticulum cell sarcoma).[19] The poorly differentiated LSA stem cells are large round or oval cells with open nuclei, a large prominent haloed nucleolus, and eosinophilic or mildly basophilic cytoplasm. Lymphoblastic LSA cells are 12 to 15 μm, have a small amount of basophilic cytoplasm and large nuclei with prominent nucleoli whereas lymphocytic and prolymphocytic LSA cells are more differentiated "mature" cells, resembling their normal counterparts but often possessing irregularly shaped nuclei. The histiocytic, histioblastic and histiolymphocytic LSA cells closely resemble the large cells lining the cortical sinuses of the lymph nodes and have a large oval nucleus, prominent nucleolus or nucleoli and abundant eosinophilic cytoplasm, which may show evidence of phagocytosis. All four histogenic cell types of LSA can occur as any of the four anatomical LSA forms (ie — multicentric, thymic, alimentary or unclassified) although the lymphoblastic type is most common and the histiocytic type occurs least frequently.

Treatment of Cats with LSA

The treatment of the majority of cats with LSA is not recommended. This is because most (70%) cats with the disease are overtly and persistently infected with FeLV (see FeLV paper) and because of the poor prognosis for cats with LSA. No treatment that is presently available can eliminate the FeLV infection or induce long disease remissions.

Although I do not recommend treatment, Hayes and MacEwen and their colleagues have been investigating different methods of treating the proliferative FeLV diseases, particularly LSA.[29] Of all these different treatments a combination chemotherapy protocol is, at the present time, probably most readily available to practitioners whose clients desire treatment for their cat. The treatment regimen is as follows: In the first week of therapy, disease remission is induced using 0.025 mg vincristine/kg body weight administered intrave-

nously together with 400 international units (I.U.) of L-asparaginase/ kg body weight given intraperitoneally. In the second week one treatment of 10 mg cyclophosphamide/kg body weight is administered intravenously and in the third week one treatment of 0.025 mg vincristine/kg body weight is given, also intravenously. In the fourth week one treatment of methotrexate (0.8 mg/kg body weight) is administered intravenously. During this four week therapy regimen prednisone (1 mg/kg body weight) is given orally, once per day, by the owner. If, at the end of the four week period, there is no tumor reduction, the four week therapy protocol outlined above is repeated. If, however, the cat is in complete remission at the end of the four week protocol, the four week treatment is repeated with two weeks of no treatment between each four week treatment period. There have been encouraging results using this protocol, but it should be stressed that the median survival time of the 62 cats that have been treated is only four months (although 20% have lived at least one year) and that all the cats remained FeLV infected even when in disease remission. One reason for the limited survival time of cats treated with this protocol is that approximately 50% of the cats with kidney LSA subsequently develop CNS metastases. In an effort to prevent metastases to the CNS, Hayes and MacEwen now treat cats with kidney LSA twice with the complete therapy regimen (presented above) and then administer the following maintenance regime for the remainder of the cat's life. First, vincristine at a dose of 0.025 mg/kg body weight is given once intravenously. Ten days to two weeks later a total dose of 30 mg/kg of cytosine arabinoside divided into four separate doses of 7.5 mg/kg is given subcutaneously every 12 hours each day for two days. Two weeks later, a single dose of 0.025 mg/kg of vincristine is again given intravenously and two weeks after that methotrexate is given once intravenously at a dose of 0.8 mg/kg. The regimen is then repeated indefinitely. Early indications are that this protocol prevents CNS metastases, but confirmation of this clinical impression awaits the conclusion of a statistical analysis that is currently in progress.

We have also been able to induce complete LSA regression in some cats by infusion of normal cat whole blood, plasma or serum and by infusing small amounts of cat serum containing high titers of FOCMA antibody [Figure 20].[30,31] However, all but one of the cats that had a complete tumor regression using these forms of immunotherapy died in a relatively short time (two to six months) due to the

residual effects of FeLV on the im-
mune system and the bone marrow.
In an attempt to overcome the dele-
terious effects of FeLV in infected cats
in remission, Jones and his col-
leagues have treated cats with LSA by
ex vivo removal of immune com-
plexes by adsorption onto *Staphlo-
coccus aureus.*[32,33] Several of these
cats have had tumor regressions and
have also rejected the virus and three
of these cats are alive and well two
and one-half years after therapy.
More research into these experimen-
tal therapeutic modalities is needed
before they can be used routinely and
effectively by veterinarians.

Prevention of LSA

Feline LSA can be prevented by
protecting FeLV uninfected unex-
posed cats from exposure to FeLV in-
fected cats. The FeLV test and removal
program has been in use for about
seven years and has effectively
eliminated FeLV from multiple cat
households and has prevented the
development of LSA in these house-
holds.[34,35] The development of a safe
and effective FeLV vaccine will, in the
future, enable LSA to be prevented
and, at present, several research
groups are testing different FeLV vac-
cines. The reader is referred to the pa-
per on the Feline Leukemia Virus in
this issue for further information on
the FeLV test and removal program
and on the research done into an
FeLV vaccine.

Public Health Considerations

Since all cases of feline LSA are caused by FeLV
and since there is concern about the public health
aspects of this virus, veterinarians should become
familiar with all of the published studies concern-
ing the public health aspects of FeLV.[4,36] A complete
literature review is presented in the paper on the
feline leukemia virus in this issue.

Plasma Cell Myeloma

Plasma cell myeloma occurs in old cats and is
a systemic neoplasm of antibody producing plasma
cells that localizes as solitary lesions or occurs as a
diffuse infiltration of the bone marrow. The spleen,
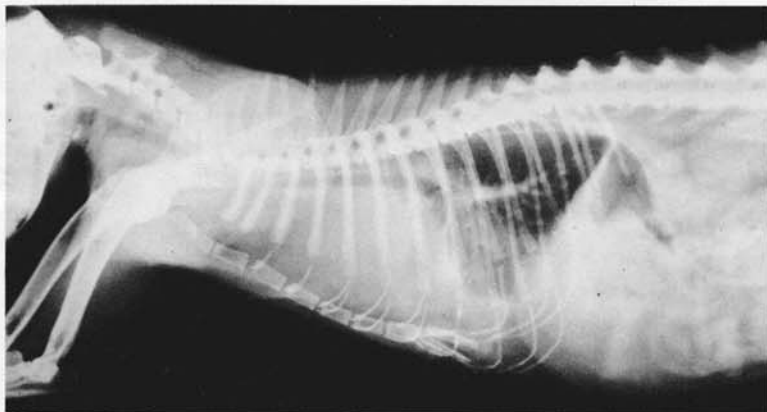liver and lymph nodes are often involved. There is
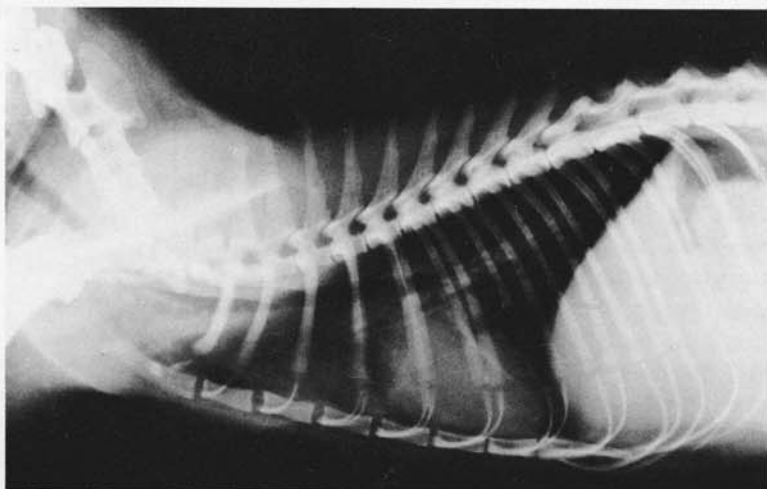

Figure 20A

Figure 20B

Figure 20— (A) Lateral radiograph of the thorax of a cat with thymic lym-
phosarcoma before therapy with serum containing FOCMA antibody.
(B) Lateral radiograph of the same cat three weeks after therapy with
FOCMA antibody was begun. Note the complete regression of the large
thymic lymphosarcoma mass.

usually a monoclonal gammopathy, and light chain
complexes (Bence-Jones protein) may be found in
the serum or urine. Plasma cell myelomas have
been reported in only three cats.[37-39] I have studied
one such case which occurred in an FeLV negative
cat which had a monoclonal gammopathy [Figure
21]. There were no punched-out bone lesions as of-
ten occur in humans and dogs with the disease.

Thymomas

The normal thymus gland is composed of lym-
phocytes that are densely packed in the cortex but
are less numerous in the medulla. The lympho-
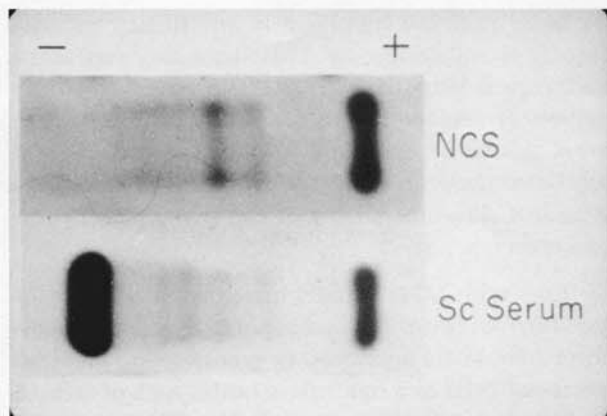cytes are supported by the epithelial network of re-

Figure 21— Electrophoretogram of normal cat serum (top-NCS) and serum from a cat with plasma cell myeloma (bottom-Sc Serum). Note the large immunoglobulin band at the negative pole (Sc serum) from the cat with plasma cell myeloma indicating a monoclonal gammopathy. (A.I. Hurvitz, Animal Medical Center)
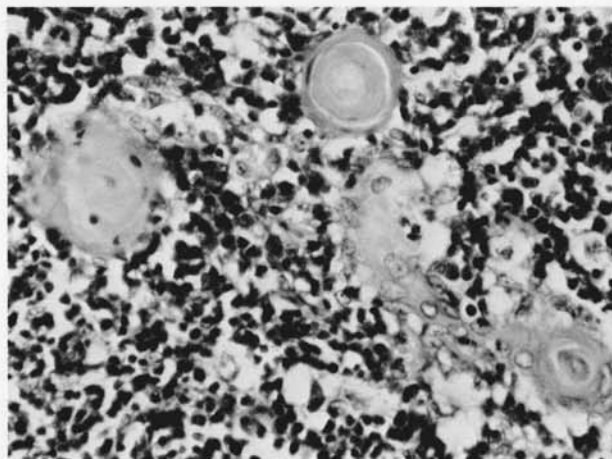

Figure 22— Thymoma, predominantly lymphocytic type. Three Hassell's corpuscles are surrounded by small, mature lymphocytes (H&E stain, 250 X) (reproduced with permission of the JAVMA).

ticular cells and fibers. Thymomas are rare, and must be distinguished from the more common thymic LSA. Thymomas are usually localized and benign tumors, in which both the epithelial and lymphoid cells proliferate.[19] The proportion of these two elements varies in individual cases which are classified according to the predominant type of cell composing the tumor.

Predominantly Epithelial Thymomas —Most thymomas are of this type and are composed of irregular masses of plump, elongated cells with abundant, faintly eosinophilic cytoplasm. No reticulum exists between the tumor cells and mitoses are rare. Lymphocytes are scattered among the epithelial cells singly and in small clusters. Fluid-containing cysts are common, but rudimentary Hassall's corpuscles are rarely present.

Predominantly Lymphocytic Thymomas —In this type of thymoma, masses of small lymphocytes are subdivided by prominent bands of fibrous tissue, and small cords or groups of epithelial cells. The lymphocytes of the tumors appear to be normal small lymphocytes and mitoses are rare [Figure 22].

Five cases of feline thymomas have been reported and I have studied an additional three cases. Two of the five published cases and two of the three cases that I studied presented with

dyspnea due to hydrothorax. Fluid removed by thorocentesis from these cats contained small, mature lymphocytes. This finding is in marked contrast to the finding of large, immature lymphocytes with vacuoles and numerous mitotic figures in the thoracic fluid of cats with thymic lymphosarcoma. Three of the eight cats with thymomas were tested for FeLV and all were FeLV negative.

Therapy

In humans, benign thymomas can generally be cured by resection or irradiation, or both.[40] Two cats with thymomas have been treated with good results.[41] One cat that was treated by resective surgery and adjunct Bleomycin lived for over one and one-half years and died of other causes. The second cat has survived for over 400 days after resective surgery and adjunct chemotherapy consisting of cytosine arabinoside 100 mg/m² SQ on days 1-4 of week 1, cyclophosphamide 50 mg/m² for days 1-4 of weeks 1-6, vincristine 0.5 mg/m² on day 1 of weeks 1-6, prednisone 20 mg/m² *bid* for week 1 then 10 mg/m² *bid* every other day and 6-mercaptopurine 50 mg/m² daily for 30 days beginning on week 6. Cats with mediastinal masses that do not yield anaplastic cells on thorocentesis should be investigated further to determine if the cells in the chest fluid are indicative of thymoma, since therapy seems to be effective in this slow growing benign tumor.
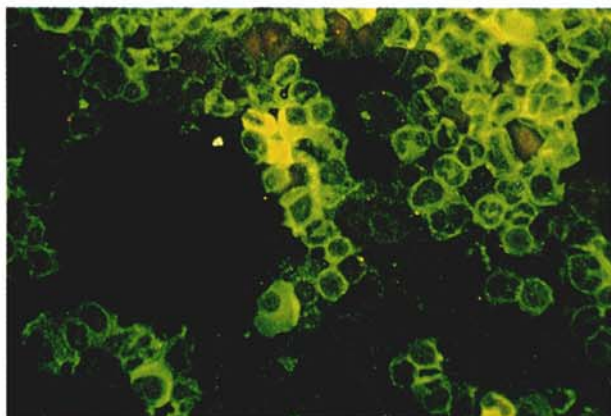
Figure 23— An FeLV positive immunofluorescent antibody test of bone marrow cells from a healthy cat. Note that all the nucleated cells of the bone marrow are infected with FeLV as shown by the apple-green cytoplasmic fluorescence.

Myeloid Tumors

Introduction

FeLV replicates in all nucleated cells of the bone marrow of cats [Figure 23].[4,27] Both proliferative (neoplastic) and degenerative (blastopenic) diseases can occur in these cells. The term "myeloproliferative" was first used by Dameshek in 1951 to indicate abnormal proliferation of a variety of bone marrow cells that leads to severe anemia and which often terminates in granulocytic leukemia.[42] Thus, myeloproliferative diseases (MPD) are a group of primary bone marrow neoplastic disorders which may involve any one or a combination of two or more cell types that originate in the bone marrow.[43] The primitive mesenchymal cell of the bone marrow gives rise to erythroblasts, myeloblasts, megakaryoblasts, osteoblasts and fibroblasts, and FeLV replicates in all of these nucleated cells and can apparently transform all of these cell types except eosinophils.[4,27]

There are four stages of myeloproliferative diseases in cats [Table 7]. The first stage is erythremic myelosis which is characterized by a marked hyperplasia of erythroid cells of the bone marrow. In the second stage there is a mixed erythroid and granulocytic precursor proliferation called erythroleukemia. The third stage is the stage in which the major proliferative cell is the myeloblast. I have observed an additional, or fourth stage, in some cats with MPD characterized by the presence of erythroid and granulocytic leukocyte precursor cells in the blood and spleen together with a proliferation of cancellous bone and/or fibrous tissues in the bone marrow resulting in medullary osteosclerosis or myelofibrosis. This stage may represent the terminal stage of feline MPD, in which the bone marrow is replaced with cancellous bone and fibrous tissue. The various MPD's listed in Table 7 may be considered to be both diseases in their own right and different stages of the overall MPD disease entity.

Cats with MPD usually have profound normocytic normochromic nonregenerative anemias with either neoplastic erythroid or granulocytic myeloid precursor cells or a mixture of both types of cells in the blood and bone marrow.[43] The PCV is usually about 9% to 10% when the cat is first seen and there is usually extramedullary hematopoiesis in the spleen, liver and lymph nodes which, if severe enough, causes splenomegaly, hepatomegaly or lymphadenopathy. Platelets are often reduced in numbers resulting in bleeding disorders and occasionally giant, abnormal platelets are present. Most cats are depressed, anorectic, have lost weight and have pale mucous membranes. Pyrexia and chronic nonhealing wounds or general secondary infections also occur, probably due to the secondary immunosuppressive effects of FeLV.

We have tested 50 cats with various cellular variants of MPD for FeLV by the immunofluorescent antibody test [Table 8].[27] Forty-six of the 50 cats (92%) with MPD were infected with FeLV and only the four cats with eosinophilic leukemia were FeLV negative. Thus, it appears that all variants of MPD of cats except eosinophilic leukemia are induced by FeLV. In support of this conclusion we have found the FeLV induced tumor-specific antigen FOCMA on the surface of erythrocytic, granulocytic and megakaryocytic leukemia cells (one case of each).[10,44] Cotter and coworkers have also reported that seven of eight cats (88%) with MPD were FeLV positive.[45] They did not report the cell types of the MPDs, thus it is not known if the only negative case was a cat with eosinophilic leukemia. Herz and his colleagues reported finding C-type virus in all five cases of MPD among which there was no case of eosinophilic leukemia.[46] It is interesting that the eosinophil appears, based on a relatively few cases, resistant to FeLV transformation even though FeLV can replicate in normal eosinophils in the blood and bone marrow.[27] Alternatively, the eosinophilic leukemias may represent another disease where FeLV can transform cells but not replicate, as occurs in 30% of feline LSAs.[2,7] An answer to this question can be obtained by testing eosinophilic leukemia cells for the presence of FOCMA.

Neoplastic FeLV Erythroid Diseases

FeLV infects and replicates well in erythroid progenitor cells, which still have nuclei, and can induce both proliferative (neoplastic) and degenerative (blastopenic) diseases of these cells [Tables 7, 8].[27] As the progenitor erythroid cells mature, the nucleus is extruded and thus the FeLV provirus and the ability of FeLV to replicate is lost. All FeLV-induced erythroid diseases occur in nucleated erythroid progenitor cells in which the FeLV provirus is present.

Reticuloendotheliosis

Proliferation of the primitive mesenchymal pluripotential stem cells can lead to an accumulation of these cells, which show no recognizable progression to a more differentiated cell type [Figure 24]. Gilmore first proposed the term reticuloendotheliosis to describe this form of MPD.[47] Cats with reticuloendotheliosis are usually anemic, and the neoplastic cells vary in size, have a reddish nucleus, a blue cytoplasm and appear to be closely related to both the erythroid and the granulocytic myeloid precursor cells.[43] Some cells contain reddish cytoplasmic azurophilic granules. The bone marrow of cats with reticuloendotheliosis contains a monotonous pattern of round, deep blue staining cells, together with an almost complete absence of mature cells of any series. Using the IFA test for FeLV we have found FeLV antigen to be present in the peripheral blood and bone marrow cells in eight out of eight cats with reticuloendotheliosis. Although C-type virus particles have been seen in cats with other MPDs (myelofibrosis and erythremic myelosis) this is the first report of FeLV infection in cats with reticuloendotheliosis.[46]

Erythremic Myelosis

The presence of abnormally high numbers of proliferating nucleated erythroid cells without significant concurrent proliferation of granulocytes is termed erythremic myelosis [Figure 25].[43,48] Thus, erythremic myelosis is a proliferative disease of only the erythroid precursor cells. The disease does not occur commonly in pet cats and is characterized by a severe anemia, marked anisocytosis without accompanying polychromasia and

Table 7

Feline Myeloproliferative Diseases

Bone Marrow Cell	Normal Cell Progeny	Myeloproliferative Disease (MPD)	MPD Stage
Primitive mesenchymal cell	All bone marrow cells listed below	Reticuloendotheliosis	I
Erythroblast	Erythrocytes	Erythremic myelosis	I
		Erythroleukemia (mixture of erythroid and myeloid cells)	II
Myeloblast	Granulocytic leukocytes	Granulocytic leukemia	III
	Monocytes	Monocytic leukemia	III
Megakaryoblast	Platelets	Megakaryocytic leukemia	III
Fibroblast	Fibroblasts	Myelofibrosis	IV
Osteoblast	Osteocytes & osteoclasts	Osteosclerosis Osteochondromatosis	IV

Table 8

Occurrence of FeLV in Feline Myeloproliferative Diseases

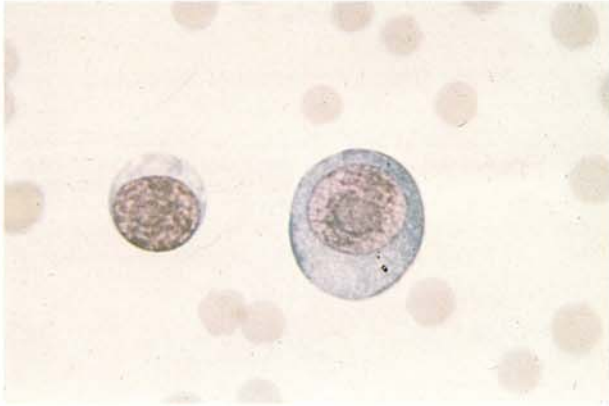| Myeloproliferative Disease	Number Tested for FeLV	Number FeLV Positive	Percent FeLV Positive
Reticuloendotheliosis	8	8	100%
Erythremic myelosis	5	5	100%
Myelogenous (granulocytic) leukemia			
Neutrophilic leukemia	4	4	100%
Eosinophilic leukemia	4	0	0%
Basophilic leukemia	1	1	100%
Erythroleukemia	7	7	100%
Megakaryocytic leukemia	1	1	100%
Osteosclerosis	2	2	100%
Myelofibrosis	4	4	100%
Cell type not classified	14	14	100%
	50	46	92%

Figure 24— Reticuloendotheliosis — note the large primitive mesenchymal pluripotential stem cell resulting from a block in the maturation process that prevents this cell from progressing to a more differentiated cell type. (Courtesy O. Schalm, U. of CA)
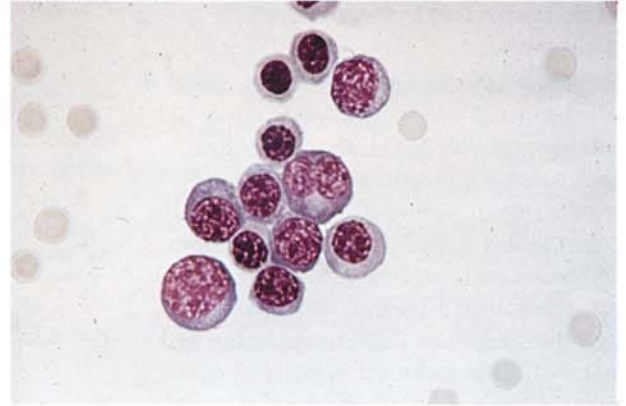

Figure 25— Erythremic myelosis — proliferation of nucleated erythroid cells without concurrent proliferation of granulocytes. Despite the presence of nucleated erythroid cells there are low numbers of reticulocytes indicating a block in maturation from the early nucleated erythrocyte to the reticulocyte. (Courtesy, O. Schalm, U. of CA)

marked variations in the numbers and morphology of the nucleated erythrocytes. The bone marrow is full of rubricytes in all stages of maturation. The anemia is a normocytic normochromic nonregenerative anemia and, even though there are nucleated erythrocytes, there is a normal or low number of reticulocytes indicating a block in maturation from the early nucleated erythrocyte to the reticulocyte. We have found FeLV antigens by the IFA test in five of five cats with erythremic myelosis [Table 8]. In addition, Herz and his colleagues have found C-type particles in a cat with erythremic myelosis.[46]

Erythroleukemia

There is no clear distinction between erythremic myelosis and erythroleukemia. However, for the purpose of classifying MPDs, the distinction between the two diseases is based on the presence of myeloblasts (granulocytic leukocyte precursors) along with abnormal nucleated erythrocytes in the peripheral blood of cats with erythroleukemia, whereas only neoplastic erythroid cells are present in cats with erythremic myelosis.[43] Most cats with erythroleukemia have a profound normocytic normochromic nonregenerative anemia and, even though nucleated erythrocytes are present there is a normal or low reticulocyte count indicating a block in the process of erythroid cell maturation. The half-life of the erythrocytes is reduced by 50% in cats with this disease. Proliferating erythroid and myeloid neoplastic cells are found in the blood,

bone marrow and in various organs such as the spleen, liver and lymph nodes [Figure 26]. We have found FeLV antigen present in the erythroleukemia cells of seven out of seven cats [Table 8] and Herz and his colleagues have found C-type particles by electron microscopy in one cat.[46]

Neoplastic Myeloid Diseases— Myelogenous (Granulocytic) Leukemias

Granulocytic leukocytes (neutrophils and basophils) can be transformed by FeLV in vivo but, in the cat, myelogenous leukemias are far less common than lymphoid malignancies.[38] Using the IFA test, I have observed that FeLV can replicate in normal and neoplastic neutrophils and in normal, but not in neoplastic, eosinophils.[7] We have found FOCMA expressed on the surface of neutrophilic leukemia cells obtained from a cat with neutrophilic myelogenous leukemia indicating that FeLV induced this disease.[10,44] One case of myelomonocytic (neutrophilic and monocytic) leukemia which was FeLV positive has also been reported.[49]

Neutrophilic Leukemia

Neutrophilic leukemia is often referred to as myelogenous leukemia or granulocytic leukemia; however, I prefer the more specific term of neutrophilic leukemia. This disease is rare although it is the most common type of myelogenous leukemia in cats. Two series of cases have been reported, one of nine cases reported by Holzworth and 14 cases reported by Schalm.[38,43] Although these studies did
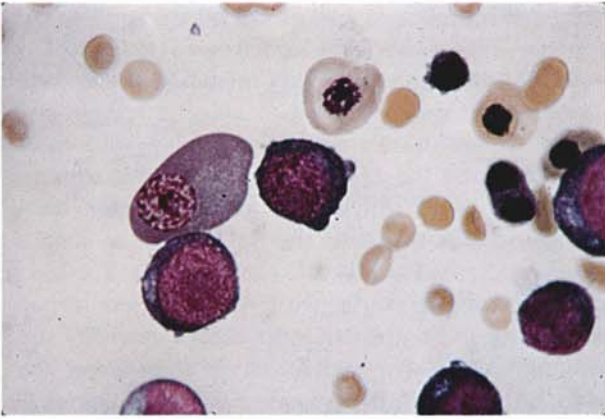
Figure 26— Erythroleukemia — proliferation of granulocytic leukocyte precursor cells along with abnormal nucleated erythroid cells. (Courtesy, O. Schalm, U. of CA)
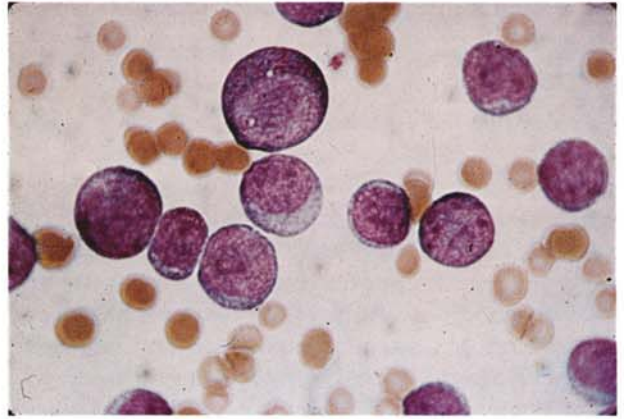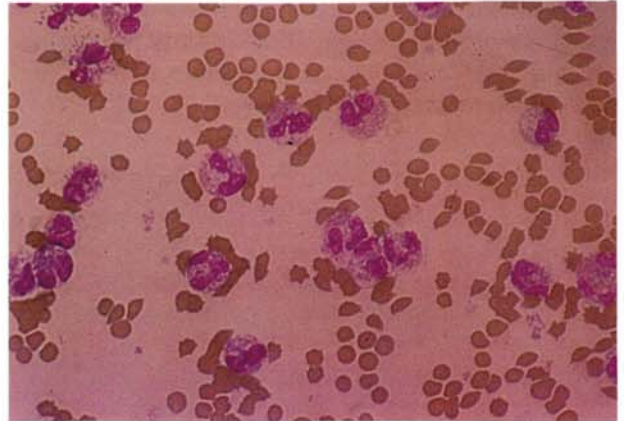

Figure 27— Neutrophilic leukemia — proliferation of neutrophilic myelocytes, progranulocytes and myeloblasts. (Courtesy O. Schalm, U. of CA)

Figure 28 (Right)— Eosinophilic leukemia — proliferation of eosinophilic myelocytes, band eosinophils and mostly mature eosinophils. (Courtesy, R. Wilkins, Animal Medical Center)

not determine the FeLV status of the cats, I have found all four cats that I have observed with neutrophilic leukemia to be FeLV positive [Table 8], and Henness and Crow have found all three of their cases to be FeLV positive.[50] In addition, Jarrett and coworkers have reported that one case of neutrophilic myelogenous leukemia was induced by experimental inoculation of FeLV into a newborn kitten. In cats with neutrophilic leukemia, the total leukocyte numbers may be below normal, but are usually increased, and neutrophilic peroxidase positive myelocytes, progranulocytes and myeloblasts are present in the blood.[51,52] There is usually splenomegaly, hepatomegaly and variable lymphadenopathy. All cats with the disease are severely anemic even though large numbers of nucleated erythrocytes are present in some cats. The bone marrow is hypercellular due to proliferation of neutrophilic leukemic cells and the M:E ratio is markedly increased [Figure 27].

Eosinophilic Leukemia

Eosinophilic leukemia is the only myeloproliferative disease of cats not known to be induced by FeLV. The disease occurs very rarely in pet cats and is characterized by an over production of eosinophils with immature forms present in the blood and various tissues [Figure 28].

Megakaryocytic Leukemia

To my knowledge there have not been any reports of megakaryocytic leukemia in cats. I have observed one case of this disease in an FeLV positive cat.[44] The cat was severely anemic and had hepatosplenomegaly. There were large numbers of bizzar platelets in the peripheral blood and a large increase in the number of megakaryocytes in the bone marrow and spleen. The megakaryocytes were tested for the FeLV induced tumor-specific antigen FOCMA and were found to be positive, indicating that this disease was induced by FeLV.

Monocytic Leukemia

Monocytes are derived from stem cells in the bone marrow and they migrate into tissues and body cavities to become "fixed" or "free" macrophages. Very few cases of monocytic leukemia have been reported in cats. The four cases that have been reported occurred in young, three to four year old, cats.[38,43] Anorexia, depression, vomiting and pyrexia were common clinical signs. Moderate to severe anemias were present, two cats had normal WBC counts, one was leukopenic and one had a severe leukocytosis (342,000/ul). All cats had evidence of monocytes in their peripheral blood ranging from 25% to 99% of the leukocytes. The cells had a limited peroxidase reaction typical of monocytes. On necropsy there was moderate to slight lymphadenopathy, nodular kidneys and many organs were diffusely infiltrated with monocytes. No FeLV tests were done on any of the cats; however, it is probable that most, if not all, of these cats were FeLV positive since all had clinical signs related to FeLV infection (anemia, one had aborted, and one had a chronic necrotic bite wound).

Myelofibrosis

I have observed four FeLV positive cats who were severely anemic and who had erythroid or myeloid precursor cells in their blood in the early stages of their disease, but then became severely pancytopenic.[21] During the pancytopenic stage no hematopoietic cells could be aspirated from the bone marrow. Necropsy of these cats revealed extensive replacement of the bone marrow with fibrous tissue (fibroblasts) and very few remaining erythroid or myeloid cells.

Herz and his colleagues have observed C-type virus particles by electron microscopy in two cats with myelofibrosis.[46] One cat had primitive atypical granulocytes and myelofibrosis in the bone marrow and liver, while in the other cat unclassified mononuclear cells were present together with extreme fibrosis of the marrow and liver. One cat became very leukopenic in the terminal stages of its disease.

Osteochondromatosis and
Medullary Osteosclerosis

Osteochondromatosis or multiple cartilaginous exostoses is a benign proliferative disease of bone known to occur in humans, dogs, horses and cats.[53] In all species except cats the disease appears to have a hereditary basis and multiple osteochondromas are usually found both in the metaphyseal regions of long bones and in flat bones such as the scapulae, ribs, pelvis and vertebrae. The growth of osteochondromas usually ceases when the growth plates close in young-adult people, dogs and horses. Osteochondromatosis of cats appears to be different since the disease occurs in mature cats about two years old whose growth plates have closed and affects mainly the flat bones, the scapulae, pelvis, ribs and skull, rather than the long bones. The growths arise from the surface of the affected bones and appear more dense than the underlying bone. Bone destruction at the base of the osteochondroma may indicate malignant transformation in the lesion. The cortex, periosteum and marrow cavity of the affected bone are continuous with the osteochondroma. While osteochondromas of other species respond to the same hormonal controls as growth plates and cease growing in synchrony with growth plate closure, feline osteochondromas grow progressively, which is a characteristic feature of tumors.

Feline osteochondromatosis has not been proven to be caused by FeLV. However, a total of eight cats have been found to have had the disease and all three cats that we studied were found to be infected with FeLV [Figure 29]. Oncovirus particles were detected in two other cats, but the remaining three cats with the disease were not examined for virus.[53] Thus, FeLV appears to be associated with osteochondromatosis, but has not yet been shown to be the cause of the disease.

Hoover and his colleagues have observed medullary osteosclerosis in 12 out of 13 kittens who developed anemias after experimental infection with FeLV.[54] Although the cortical bone was normal, there was an increase in the amount of cancellous bone in the marrow cavities. C-type viral particles were seen in osteocytes, osteoblasts and megakaryocytes and FeLV antigen present in the peripheral blood leukocytes. Both Hoover's group and my group have observed similar lesions in pet cats with naturally occurring FeLV anemias [Figure 30].[54] Feline medullary osteosclerosis is similar to the osteosclerosis seen in avian leukosis virus-induced anemias of chickens.[55]

In addition to these proliferative bone lesions of the marrow cavity and periosteum, Qureshi and Olander have reported the presence of heterotopic (misplaced) bone in the LSA tissues of two cats.[56] There was mature osseous tissue surrounding marrow cells in the LSA tissue of one of the cats and osseous tissue without marrow cells in the other cat.

Figure 29— Multiple osteochondromas in the flat bones, pelvis, ribs and scapulae, of an FeLV infected cat.

Figure 30 (Right)— Medullary osteosclerosis — note the thickened cortices and trabecular bone filling the femoral medullary cavities.

Osteochondromatosis and medullary osteosclerosis may be induced by FeLV stimulation or transformation of periosteal fibroblasts or medullary osteocytes and osteoblasts resulting in excess cartilage, bone or fibrous tissue proliferation. However, the etiologic association of FeLV with these conditions remains to be elucidated.

Myelofibrosis and medullary osteosclerosis may represent the final stages of reactive bone marrow cells in FeLV induced MPD. It seems apparent that FeLV can transform and cause proliferative neoplastic changes in all bone marrow cells, except possibly eosinophils. The first cells to respond appear to be erythroid cells (erythremic myelosis), followed by the granulocytic leukocytes (erythroleukemia and granulocytic leukemia). Finally the stromal elements proliferate causing myelofibrosis and medullary osteosclerosis which causes a pancytopenia. FeLV therefore offers an excellent probe with which to study the effects of an RNA tumor virus on bone marrow cells ranging from the primitive mesenchymal stem cell to stromal bone and connective tissue cells.

Conclusion

Hematopoietic tumors are the most common single group of feline tumors and account for a significant number of deaths due to disease in the pet cat population. The research done during the last 10 years has shown that FeLV causes almost all of these tumors and that their development in pet cats can be prevented by the strict implementation of procedures to isolate FeLV infected cats from uninfected cats. It is now known that FeLV also causes degenerative lymphoid and myeloid diseases and, in fact, these diseases are more common than the FeLV-induced neoplastic diseases. The FeLV-induced degenerative hematopoietic diseases are the subject of the following paper in this special issue.

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