Feline Leukemia Virus Non-Neoplastic Diseases

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The feline leukemia virus (FeLV) causes degenerative (non-neoplastic), as well as proliferative (neoplastic) diseases of the cell types that it infects. Thus, FeLV may cause thymic atrophy, a degenerative disease of thymic lymphoid cells, nonregenerative anemia, a degenerative disease of the red blood cells or myeloblastopenia, a degeneration of the granulocytes. In addition, FeLV is indirectly responsible for numerous secondary infectious diseases since it suppresses the ability of the immune system of the cat to respond to infectious agents. The non-neoplastic FeLV diseases are all progressive and fatal, and together account for more cat deaths than does lymphosarcoma. The degenerative FeLV diseases may be diagnosed by means of routine hematological and/or histological methods and a positive FeLV test, and can be prevented by the FeLV test and a removal program.

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Introduction

FeLV grows best in rapidly dividing cells, such as lymphocytes, granulocytic leukocytes and erythroid progenator cells, and causes neoplastic diseases by inducing uncontrolled proliferation of these cells, or more commonly, causes degenerative blastopenic diseases by damaging these cells in some way [Table 1]. For example, lymphosarcoma (LSA) is a malignant disease of lymphocytes, (usually thymic (T) cell in origin) whereas thymic atrophy is a degenerative disease of the thymic (T) lymphocytes. Similarly, FeLV-induced proliferative changes in the red blood cell precursors result in erythremic myelosis while FeLV-induced degenerative changes result in anemias. Many pet cats with FeLV diseases have, in addition to their FeLV disease, anemia due to the effect of FeLV in the bone marrow.[1,2] Thus, many cats with lymphosarcoma or myeloproliferative diseases or immunosuppressive diseases are anemic. In addition to secondary anemia, that is present concurrently with an FeLV disease, the virus can induce a primary anemia, that is, an anemia caused by FeLV but with no other concurrent FeLV disease [Table 2].

The FeLV panleukopenia-like disease is a degenerative disease of granulocytes, while myelogenous leukemia is a malignant proliferation of the granulocytes.[2] FeLV is also associated with, but has not yet been proven to cause fetal abortions and resorptions.[2,3] In addition, FeLV is immunosuppressive[4,5] and is thus indirectly responsible for numerous secondary infectious diseases.[1-3] In fact, more cats die of these FeLV associated immunosuppressive diseases than die of LSA. In very rare instances FeLV can combine with cat cellular genes to produce the feline sarcoma virus (FeSV) which infects and transforms fibroblasts and causes multicentric fibrosarcomas in young cats. (See paper of the feline sarcoma virus in this issue).

Table 1

FeLV Diseases

Cell Type	Proliferative Diseases (Neoplastic)	Degenerative Diseases (Blastopenic)
1. Diseases known to be caused by FeLV		
A. Lymphoid cells	Lymphosarcoma Reticulum cell sarcoma	Thymic atrophy (kittens) Immunosuppressive diseases (adults)
B. Bone marrow cells		
1. Primitive mesenchymal cell	Reticuloendotheliosis	—
2. Erythroblast	Erythremic myelosis	Erythroblastosis (regenerative anemia)
	Erythroleukemia	Erythroblastopenia (nonregenerative anemia)
		Pancytopenia
3. Myeloblast	Granulocytic leukemias (neutrophilic) (basophilic)	Myeloblastopenia (panleukopenia-like syndrome)
4. Megakaryocyte	Megakaryocytic leukemia	Thrombocytopenia
5. Fibroblast	Myelofibrosis	—
6. Osteoblast	Medullary osteosclerosis Osteochondromatosis	—
C. Kidney	—	FeLV immune complex glomerulonephritis
2. Diseases thought to be caused by FeLV		
A. Placenta and uterus	—	Abortions & resorptions
B. Neural cells	—	Neurologic syndrome
3. FeSV disease (FeSV is derived from recombination of FeLV with cat cellular genes.)		
A. Skin fibroblast	Multicentric fibrosarcoma	—

Degenerative FeLV Lymphoid Diseases

FeLV-induced immunosuppression is probably the most frequent deleterious effect and cause of death in FeLV infected cats. Persistently (lifelong) infected pet cats may be immunosuppressed because of: 1) FeLV antigen-antibody immune complex formation, 2) FeLV-induced lymphopenia or neutropenia or, 3) FeLV-induced immune cell dysfunction (see paper on the Feline Leukemia Virus).

Thymic Atrophy

Thymic atrophy is a degenerative lymphoid disease that can be induced experimentally by inoculating FeLV into young kittens[6] and the disease occurs naturally in FeLV infected pet kittens born from FeLV infected queens or in kittens infected early in life by exposure to other infected

Table 2

Classification and Characteristics of FeLV Anemias

1. Secondary FeLV Anemias
   - A. Concurrent with FeLV diseases
     1. Lymphosarcoma
     2. Myeloproliferative diseases
     3. FeLV immunosuppressive diseases
2. Primary FeLV Anemias
   - A. FeLV Erythroblastosis
     1. Regenerative anemia—megaloblastic anemia
     2. Erythroid cells regenerating—normoblasts and reticulocytes increased in numbers
     3. This FeLV anemia is often transient and may lead to a terminal nonregenerative anemia or myeloproliferative disease.
   - B. FeLV Erythroblastopenia (pure red cell aplasia)
     1. Only erythroid cells are degenerative—it is a nonregenerative normocytic normochromic anemia.
     2. Leukocytes and platelets are normal.
   - C. FeLV Pancytopenia (aplastic anemia)
     1. All hematopoietic cells are degenerative (combined erythroblastopenia and myeloblastopenia).
     2. Erythroid cells are degenerative causing a nonregenerative normocytic normochromic anemia.
     3. Granulocytic leukocytes are degenerative causing a leukopenia.
     4. Platelets are decreased in numbers.

Figure 1— Thymic atrophy—a typical example of a young kitten with thymic atrophy. Such kittens are runted, have a rough hair-coat and do not nurse vigorously.

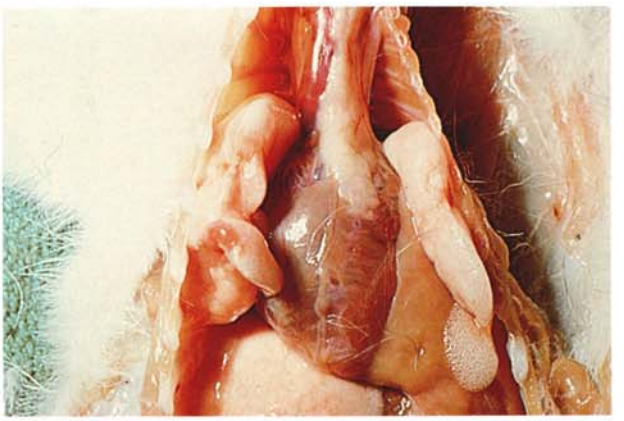

Figure 2— Thymic atrophy—only a small remnant of thymus persists in an FeLV-infected kitten that died of a secondary disease resulting from immunosuppression caused by FeLV-induced thymic atrophy.

cats.[2,3,7,8] To date we have found that 14 of 16 kittens with thymic atrophy that we studied were FeLV positive. The virus destroys the T-lymphocytes in the thymus and other lymphoid tissues resulting in a defective cell mediated immune response.[4-6] FeLV infected kittens are thus susceptible to secondary infectious diseases caused by viruses, bacteria or fungi and are often stunted and die of secondary infections, usually bronchopneumonia and enteritis, within a few weeks of birth. At necropsy, little or no thymic tissue is present and histologically there is atrophy of the thymus [Figures 1, 2, 3].[6]

FeLV Associated Immunosuppressive Diseases

FeLV is immunosuppressive in adult cats as well as in kittens[24] and many of these cats develop chronic secondary diseases which are nonresponsive to therapy [Figures 4, 5, 6].[1,2,8-11] In fact, more cats die of FeLV associated chronic immunosuppressive diseases than die from LSA [Table 3]. Approximately 50% of cats with feline infectious peritonitis, chronic stomatitis, chronic gingivitis, or chronic oral ulcers are infected with FeLV, as are about 40% of cats with chronic abscesses or nonhealing wounds of the skin.[8] Over half of the cats with chronic upper respiratory infections and about 60% of the cats with chronic nonresponsive infections and septicemia are infected with FeLV. FeLV does not cause these disorders directly but renders the infected cats more susceptible to secondary infections and to the consequences of these infections due to its immunosuppressive effects.

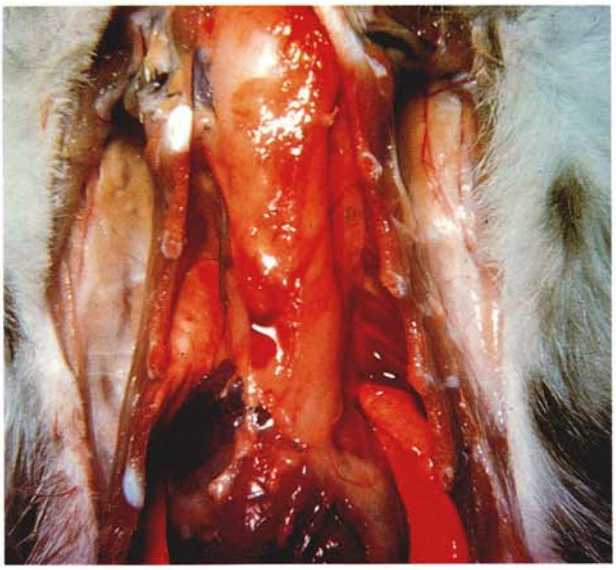

Figure 3— Normal thymus—a normal, large, firm thymus in a healthy FeLV-uninfected kitten.

FeLV Degenerative Diseases of the Bone Marrow (Myelodegenerative Diseases)

FeLV replicates in all nucleated cells in the bone marrow and can cause degenerative disease in each cell type.[12] Thus, infected erythroid cells and granulocytic leukocytes can become depleted in infected cats. In addition to depletion of these cells the number of platelets can be severely reduced in some infected cats. The mechanism by which FeLV causes degenerative bone marrow diseases is unknown, but three possibilities exist. The

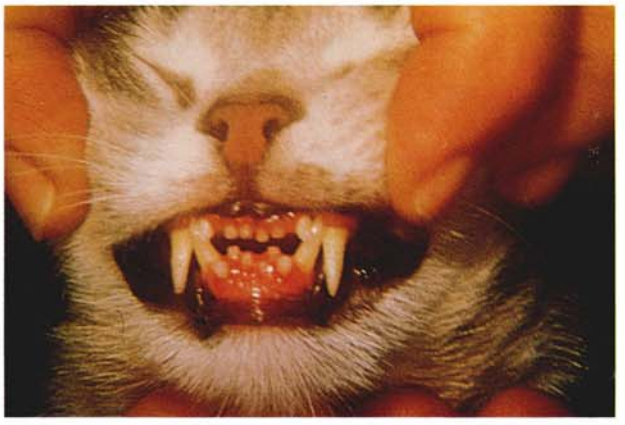

Figure 4— Gingivitis — severe chronic gingivitis in this FeLV infected cat occurred because of the immunosuppressive effects of FeLV.

Figure 5— A chronic nonhealing wound of the skin below the ear of a persistently FeLV-infected cat.

first possibility is that FeLV causes lysis by damaging the infected cell's membrane, possibly by the process of budding. The second possibility is that FeLV may antigenically alter the cell membrane, by budding or by inducing FOCMA, and the altered membrane may then be lysed by antibody to FeLV or to FOCMA[13] or lysed by killer lymphocytes. Lastly, FeLV may affect effector cells such as erythropoietin producing cells which then may not produce sufficient erythropoietin resulting in erythroid depletion. FeLV-induced degenerative bone marrow diseases occur far more commonly than FeLV-induced myeloproliferative diseases.[1]

FeLV Erythroid Degenerative Diseases

Primary FeLV Anemias

Cats are more susceptible to anemias than most other species because their erythrocytes have a shorter life span, 70 to 80 days compared to the erythrocyte life span of 120 days for most other species.[14] The erythrocyte turnover is higher in the cat which means that disturbances in erythropoiesis are recognized sooner. FeLV is the major cause of anemias in pet cats and anemia is the most common effect of FeLV infection.[1,2]

There are three distinct types of primary FeLV-induced anemias. They are: 1) FeLV erythroblastosis (regenerative anemia), 2) FeLV erythroblastopenia (nonregenerative anemia) and 3) FeLV pancytopenia. Cats can die of any of these three types of anemia but often they develop all three anemias in sequence, beginning with erythroblastosis which

Figure 6— A cat with chronic bacterial upper respiratory disease secondary to FeLV-induced immunosuppression.

leads to erythroblastopenia and finally to a pancytopenia and death. These phases indicate that FeLV has an initial stimulatory effect on the erythroid cells followed by a degenerative effect. Since most cats do not reveal signs of any illness until the disease is in the advanced stages, most anemic pet cats are brought to veterinarians in the erythroblastopenia stage after having already passed through the erythroblastosis anemic stage.

Table 3

Occurrence of FeLV in Cats with Chronic Immunosuppressive Diseases

Disease	Number of Cats Tested	Number FeLV Positive	% FeLV Positive
Feline infectious peritonitis	140	64	46%
Chronic stomatitis & gingivitis	347	168	48%
Poor healing wounds & abscesses	233	80	34%
Chronic respiratory diseases	64	35	55%
Chronic general infections	56	32	57%
	840	379	45%

Experimental FeLV Anemias

Mackey and co-workers showed, in a limited study, that the Glasgow strains of FeLV serotypes A, AB, B and C induced different types of anemias in kittens.[15] FeLV-A and FeLV-AB induced transient nonfatal macrocytic normochromic anemias with normoblastosis and reticulocytosis (erythroblastosis). There was extensive splenic extramedullary hematopoiesis and the anemias were of the hemolytic type. In contrast, FeLV-C induced a fatal aplastic or nonregenerative normocytic normochromic anemia. No anemias developed in kittens inoculated with FeLV-B alone. Thus, experimentally, two of the three FeLV subgroups have been found to be capable of inducing anemias. Similarly, Hoover and co-workers induced fatal nonregenerative anemias[16] by inoculating day-old SPF kittens with FeLV-ABC from FL-74 cells.[17] The nonregenerative anemias developed 10 to 14 weeks after inoculation and four weeks after FeLV antigens were detectable in the peripheral blood leukocytes by immunofluorescence.[12] There were marked decreases in the number of lymphoid and myeloid cells in these kittens as evidenced by thymic atrophy, lymphoid depletion in the cortical and paracortical areas of lymph nodes and marked hypoplasia of the erythroid cells of the bone marrow. There was a neutropenia in many of the cats, and erythrophagia and hemosiderosis occurred in the spleen and lymph nodes but, in contrast to the Glasgow study, there was no extramedullary hematopoiesis in the spleen or liver.

Naturally Occurring Anemias of Pet Cats

FeLV Erythroblastosis

FeLV regenerative anemia, erythroblastosis, is not as common a disease entity as FeLV-erythroblastopenia or FeLV-pancytopenia. Only about 15% of FeLV infected anemic pet cats that we have studied, 18% of those studied by Cotter[18] and 17% of those FeLV infected anemic cats studied by Maggio[14] had regenerative anemias. Cats with regenerative anemias are listless, have pale mucous membranes, cannot tolerate exercise and have low PCVs and RBC counts along with immature or "responding" erythrocytes. The immature erythrocytes which are rushed out of the marrow in response to the FeLV anemia are polychromatophilic macrocytic cells [Figure 7] and there is an increase in the number of reticulocytes and nucleated red blood cells in the blood and bone marrow. Extramedullary hematopoiesis occurs in the spleen and liver. Cats with non-FeLV induced regenerative anemias usually have a good prognosis whereas FeLV infected cats with regenerative anemias (erythroblastosis) do not have good prognoses since many of them eventually develop the fatal erythroblastopenia or pancytopenia syndromes and some even develop myeloproliferative disease or lymphosarcoma.

FeLV Erythroblastopenia
(FeLV Nonregenerative Anemia)

FeLV erythroblastopenia, also known as pure red cell aplasia, is a specific disease caused by FeLV in experimentally inoculated kittens[15,16] and in pet cats.[14,18] We have tested 215 cats with either erythroblastopenia or pancytopenia (all with nonregenerative anemias) and found 147 (68%) of the cats to be FeLV positive. Similarly, in a separate study Cotter reported that 70% of anemic cats were FeLV infected.[18]

Erythroblastopenia is a progressive and fatal degenerative disease of only the erythroid cells. The anemia is normocytic and normochromic [Figures 8, 9] indicating a nonregenerative anemia. Cats with nonregenerative anemias have a poor prognosis because they are unable to respond to their anemic state by producing more erythrocytes. The leukocytes are normal or may even be elevated and there are usually normal numbers of platelets. This disease is common in FeLV infected cats, in fact, more infected pet cats develop erythroblastopenia than develop lymphosarcoma.[8]

Cotter has studied 100 pet cats with anemias (PCVs below 20%) all of which had no other obvious

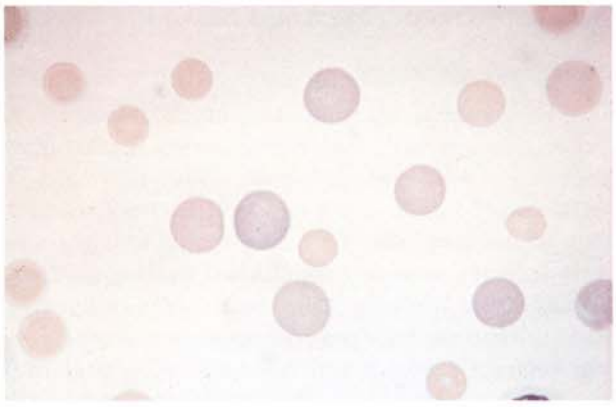

Figure 7— FeLV erythroblastosis — regenerative anemia in an FeLV infected cat. Note the large polychromatophilic macrocytic erythrocytes indicative of regenerative anemia. (Courtesy O. Schalm, U. of Calif.)

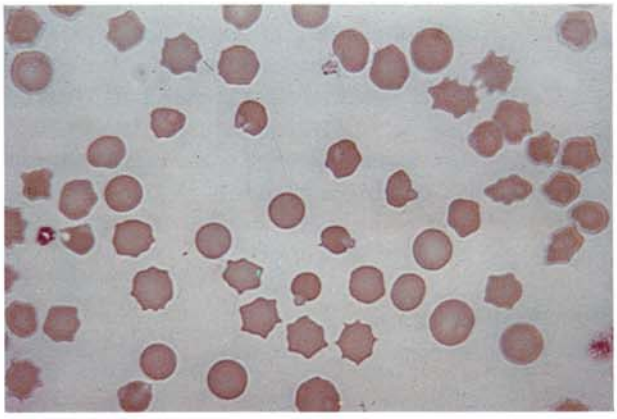

Figure 8— FeLV erythroblastopenia — nonregenerative anemia in an FeLV infected cat. No immature or regenerative erythrocytes are present indicating nonregenerative anemia. Erythroblastopenia is the most common type of FeLV-induced anemia. (Courtesy O. Schalm, U. of Calif.)

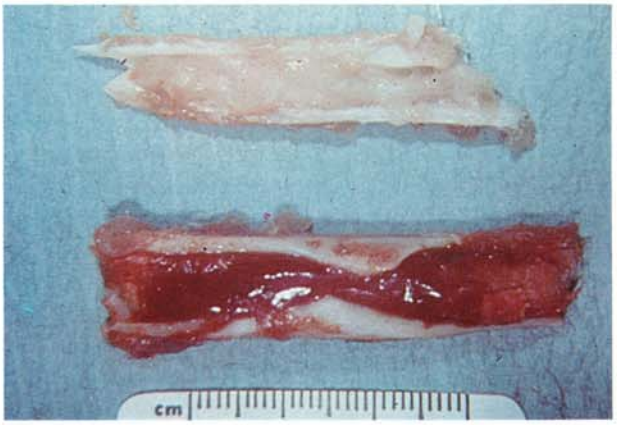

Figure 9— A pale FeLV erythroblastopenic bone marrow (top) indicative of the lack of hemoglobin-containing erythroid cells, compared with a red bone marrow from a normal cat (bottom).

disease such as lymphosarcoma, hemobartonellosis or renal disease which might have caused the anemias.[18] All cats were found to be positive for FeLV in our laboratory by the IFA test done on peripheral blood leukocytes.[12] Eighty-two percent of these 100 cats had nonregenerative anemias (erythroblastopenia) and only 18% had regenerative anemias (erythroblastosis). The mean age of the FeLV infected anemic cats was 2.7 years. Thirty-one cats had splenomegaly and 10 were icteric. The mean PCV was 9% (3%-19%) and the mean WBC count was 10,617/mm^3 (880-88,990/mm^3). Thus, some anemic cats whose WBC counts were below 8,000/mm^3 had the FeLV induced pancytopenia. Nucleated RBCs were present in the blood of 49 cats, but, with low reticulocyte counts, the presence of nucleated RBCs does not indicate a responding anemia. Of the 40 cats which had bone marrow examinations, 25 had an increased M:E ratio indicating erythroid hypoplasia. Forty-nine cats were treated with transfusions and prednisone and the median survival time was only four months although one of the treated cats reverted from FeLV test positive to FeLV negative.

Most FeLV anemic cats have erythroblastopenia either as a primary disease or along with other FeLV diseases such as lymphosarcoma or myeloproliferative diseases.

FeLV Pancytopenia

FeLV pancytopenia is the second most common form of primary FeLV myelodegenerative anemia. FeLV pancytopenia has also been called aplastic anemia. In this disease, all hematopoietic cells, both erythroid precursors and granulocytic leukocytes and megakaryocytes, are degenerative. These cats have similar signs to those of cats with erythroblastopenia. There is a normocytic normochromic nonregenerative anemia, a leukopenia [Figure 10] and a decreased number of platelets. Many of these cats have recurrent secondary diseases due to their low leukocyte counts.[18] FeLV pancytopenia can lead to myelofibrosis before death in some cats.

FeLV Myeloid Degenerative Disease

FeLV Myeloblastopenia
(Panleukopenia-like Syndrome)

The FeLV myeloid degenerative disease, myeloblastopenia, is more common than the proliferative myeloid disease, myelogenous leukemia.[1,2,8] We have found that 15 of 19 (79%) cats with myeloblastopenia were FeLV positive. Although this

syndrome resembles panleukopenia (feline distemper) it occurs in FeLV infected cats that are immune to the panleukopenia virus. FeLV infected healthy cats that are stressed by such things as cat fights or hospitalization often develop this syndrome two to three weeks after the stress. FeLV myeloblastopenia is characterized by dysentery, anorexia, and vomiting. A hematological examination reveals a very low white blood cell count (300-3,000/mm^3) but, in contrast to the disease panleukopenia, anemia may also be present. The characteristic bone marrow finding is hypoplasia of the granulocytic leukocytes. There is lymphoid depletion and hemorrhagic necrosis in the mesenteric, cecal, colonic and sublumbar lymph nodes [Figure 11]. Erosion of the epithelium of the tips of the intestinal villi of the small bowel occurs which is different from that which occurs in the crypts of the villi in feline distemper. Once the disease develops, the white blood cell count remains depressed and the cat will eventually die despite supportive therapy. I have experimentally induced this disease with FeLV in adult cats.

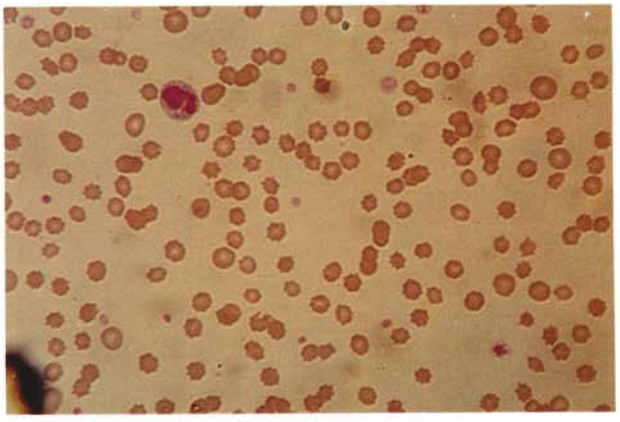

Figure 10— A blood smear from a cat with FeLV pancytopenia (panmyelosis). This cat is erythroblastopenic and is panleukopenic (pancytopenic).

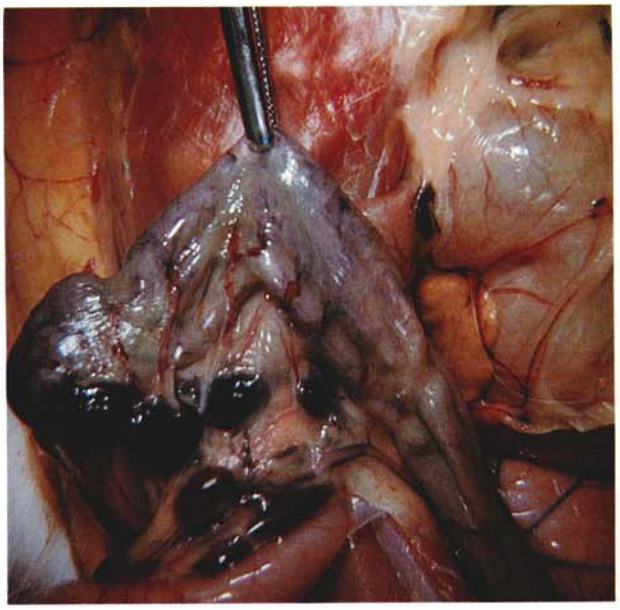

Figure 11— FeLV myeloblastopenia (panleukopenia-like syndrome). The colonic lymph nodes are hemorrhagic and there is a severe hemorrhagic enteritis.

Other FeLV Degenerative Diseases

FeLV Immune Complex Glomerulonephritis

Glomerulonephritis is an inflammatory degenerative disease of the renal glomeruli. The glomeruli are responsible for filtering the blood to produce urine. There are several causes of glomerulonephritis among which is the deposition of immune complexes on the glomerular capillary basement membrane. Continual formation and circulation of complexes is necessary for disease production and the proportion of antibody and antigen in the immune complexes influences their deposition in the glomerular capillaries.[19] Small immune complexes, which form in antigen excess or if the antibody has a low affinity or is a nonprecipitating antibody, are more nephrotoxic than large immune complexes. After the deposition of immune complexes in the glomerular capillary basement membranes, complement is fixed to the complexes releasing chemotactic factors which attract granulocytes. The granulocytes release their lysosomal enzymes and contribute to the acute inflammatory response of immune complex glomerulonephritis.

An association between membranous glomerulonephritis and lymphoid malignancies and other tumors has been noted in humans[19] and in mice.[20] For example, nearly all leukemic AKR mice have immune complex glomerulonephritis although less than 20% manifest clinical renal disease. In addition, NZB mice which are chronically infected with MuLV have a high incidence of glomerulonephritis.[21] Both the AKR and NZB mice have MuLV antigens, antibody and complement deposited as immune complexes in their glomeruli.

The life long FeLV viremia of persistently infected pet cats offers ideal conditions for the development of immune complexes.[1,12,19] FeLV replication produces a continuous supply of soluble viral antigens[22] over a long period of time and these antigens occur in excess of antibody,[23] thus encourag-

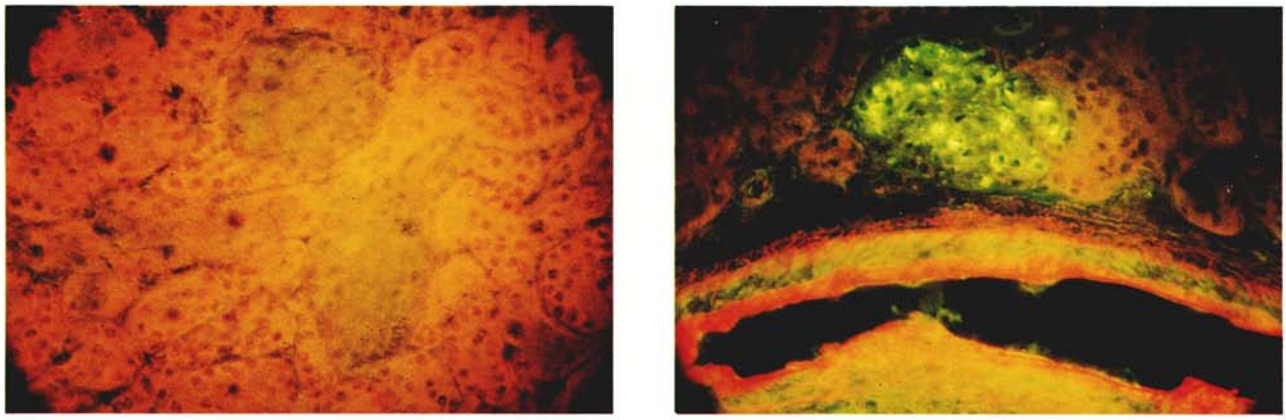

Figure 12— Indirect immunofluorescent antibody test for FeLV showing: (A, Left)— normal kidney — two glomeruli are visible, and (B, Right)— FeLV immune complex deposition in a glomerulus of a persistently FeLV infected cat. IgG and complement molecules complexed with FeLV antigens were also detected in this glomerulus.

ing the formation of the more nephrotoxic small immune complexes. Using the very sensitive Notkin's technique[24] we have found that six out of 12 persistently viremic cats have circulating immune complexes consisting of whole infectious FeLV complexed with cat IgG.[25] We have also found that three out of 12 FeLV infected cats with LSA had FeLV internal structural antigens complexed with IgG and complement deposited in their glomeruli.[19] In addition, we have shown that cats with LSA are deficient in total hemolytic complement which may indicate complement consumption by immune complexes.[26]

Cotter, Essex and I have reported that four out of five chronically FeLV infected cats had fatal glomerulonephritis without any other FeLV disease such as LSA or anemia.[3] The four cats had persistent proteinuria and three had a nephrotoxic syndrome characterized by hypoproteinemia, especially hypoalbuminemia, dependent edema and progressive uremia. Anderson and Jarrett reported that three out of 21 pet cats had membranous glomerulonephritis, in addition to their LSA.[27] Similarly, Ward and his colleagues reported a case of membranous glomerulonephritis in a cat with myeloid leukemia.[28] Jakowski and co-workers have observed a high incidence of glomerulonephritis in cats in a household where numerous cats were infected with FeLV.[29]

Thus, many persistently FeLV infected cats generate circulating FeLV immune complexes that become deposited in their glomeruli [Figures 12A, 12B] but only a relatively few cats develop signs referable to their glomerulonephritis and even fewer of these cats die from this FeLV disease.[19]

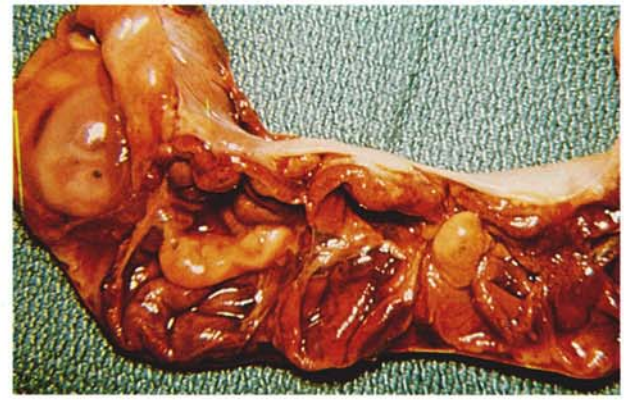

Figure 13— FeLV resorption syndrome — there are multiple resorbing fetuses in the uterus of this FeLV infected cat.

Diseases Associated with, but Not Proven to Be Caused By FeLV

Abortion and Resorption Syndromes

FeLV is thought to cause fetal abortions or resorptions late in gestation (the last two weeks). The virus was found in 209 of 307 (68%) healthy infected queens that had aborted or resorbed their fetuses, but FeLV has not been shown experimentally to cause abortions or resorptions.[2,25,30] However, it is thought that FeLV somehow damages the maternal-fetal attachment and FeLV infected queens often have a history of chronic abortions and resorptions [Figure 13].

FeLV Neurologic Syndrome

We have observed that pet cats with posterior paresis, paralysis or tetraplegia are often infected with FeLV. These cats usually show progressive fore

and/or hind leg weakness leading to eventual paralysis. Although some cats with this syndrome have focal areas of LSA compressing the spinal cord[31] or peripheral nerves, other cats had no evidence of LSA. Our observations are of interest because Gardner and his colleagues have found a murine leukemia virus-induced non-neoplastic neurologic disease in wild mice.[32] The disease occurred in 2% of wild mice one year of age or older. The lesions in the anterior lateral horns of the lumbosacral spinal cord consisted of spongiosis, gliosis and vacuolar neuronal degeneration without inflammation.[32] C-type virus particles were prevelant in the extracellular spaces of the neurophil and were occasionally seen budding from neurons, glia and endothelia.

It is not known if FeLV directly causes the neurologic syndrome seen in FeLV infected cats. However, FeLV may damage nerve tissues or induce microfoci of LSA which in turn grow and damage the tissues. More extensive histopathological studies are needed to determine the role, if any, of FeLV in this syndrome.

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