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Neoplasia associated with feline immunodeficiency virus infection in cats of Southern California

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Summary: *Between 1988 and 1991, feline immunodeficiency virus (FIV) infection status was evaluated in 1,160 cats examined at an oncology referral and general practice in Los Angeles, California. Twenty-nine (2.5%) cats were FIV positive. Neoplasia was present in 18 of the 29 (62%) cats. Sampling for neoplasia was intentionally biased in the oncology referral group. However, 33% (6/18) of FIV-infected cats with neoplasia originated from the general practice. Three neoplastic processes were observed; myeloproliferative disease (MPD; 5/18), lymphoma (LSA; 5/18), and squamous cell carcinoma (SCC; 7/18). One cat had LSA and SCC.*

Extranodal sites of LSA were common (66%) in FIV-infected cats. Sites of LSA were submandibular and mesenteric lymph nodes, liver, kidneys, periorbital area, and diffuse (heart, pancreas, bladder). Sites of SCC were sublingual (n = 2), nasal planum (n = 3), nasal planum and eyelids (n = 1), and mandible (n = 2). Feline leukemia virus co-infection was observed in 17% (5/29) of FIV-infected cats. The FIV-infected cats with MPD were young (range, 8 months to 13 years; median, 4 years) and had short survival duration (2, 6, 21, 134, 249 days) even in response to aggressive treatment. The FIV-infected cats with LSA were older (median age, 8 years; range, 4 to 14 years) and survived 60 days if untreated. Cats administered chemotherapy survived 39, 45, 217, and 243 days; the latter 2 cats had partial remission of 2 months' duration. Older FIV-infected cats had SCC (median age, 12 years; remission range, 7 to 16 years) because of more frequent association of both diseases in older cats with outdoor environment.

Lymphocytic-plasmacytic lymphadenopathy was seen in 10 necropsied FIV-infected cats (4 without neoplasia, 3 with LSA, 1 with SCC, and 2 with MPD). Lymphadenopathy associated with FIV may develop in one lymph node, and lymphoma may develop in another lymph node. Clinically, FIV-induced lymphadenopathy may be confused with progressive lymphoma.

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Feline immunodeficiency virus (FIV) is a lentivirus that is distantly related to the human (HIV)

and simian immunodeficiency viruses (HIV and SIV, respectively).[1-3] Similar to HIV, FIV has been associated with higher incidence of lymphoma (LSA) and myeloid tumors (myelogenous leukemia, myeloproliferative disease, myelodysplastic disorders—MPD).[4,a] Neoplasia is the sole illness in 1 to 21% of FIV-infected cats.[4-9,a] Both viruses (FIV and FeLV) have been shown to act synergistically to cause higher incidence of LSA and MPD.[4,b]

A review of the literature indicates the wide geographic area (Japan, Australia, Europe, North America) and small numbers of LSA and MPD reported.[4-19,a-e] The purpose of the study reported here was to evaluate the clinical course, and epidemiologic and histopathologic features of naturally acquired infection in FIV-infected cats with neoplastic diseases.

Materials and Methods

Between July 1988 and January 1991, 1,160 cats in Southern California were screened for FIV-infection by use of an ELISA.[d] An intentional sampling bias for neoplastic disease was evident; 394 (34%) cats had been referred because of suspected neoplasia. Feline leukemia virus ELISA[e] were performed on all cats. Western blot for FIV[f] was performed on 17 of the 29 FIV (ELISA)-positive cats. Complete necropsy was performed on 14 of 20 cats, whereas the remaining cats had antemortem true-cut or excisional biopsy.

Treatment was supportive medical care: fluid therapy, antibiotics, force feedings, appetite stimulants, analgesics, multiple transfusions, and erythropoeitin.[g] Cats with LSA were treated by use of conventional chemotherapy: cyclophosphamide[h] (50mg/m^2 of body surface, PO, q 48 h), prednisone[i] (1mg/kg, PO, daily for 7 days, then 0.05mg/kg, PO q 48 h), and vincristine[j] (0.05mg/m^2, IV weekly for 6 weeks). Maintenance treatment consisted of pulse cycles for 2 consecutive weeks of treatment followed by 2 weeks of no treatment. Periorbital lymphoma (cat 10) was treated with combination doxorubicin[k] (20mg/m^2, IV, q 4 wk) and orthovoltage radiation[l] (450 cGy weekly for 5 treatments). Remission was defined as 50% reduction in tumor size for 2 weeks. Cats 14 and 15 had SCC of the mandible treated by hemimandibulectomy and radiation therapy. In 6 of 18 cases, owners decided against treatment and these pets were euthanatized because of anorexia or signs of neurologic dysfunction. Two survival times were calculated: from FIV diagnosis to death and from neoplasia diagnosis to death.

Table 1—Feline immunodeficiency virus (FIV)–infected cats with neoplasia, grouped by type of practice (Referral vs general practice) population

Cats		
Neoplasia referral	General practice	Disease
2	3	MPD
4	2	LSA
6	1	SCC
12	6	Totals

MPD = myeloproliferative or myelodysplastic diseases; LSA = lymphoma; SCC = squamous cell carcinoma.

Table 2—Summary of serodiagnostic testing performed on FIV-infected cats with neoplasia

Cat No.	FeLV ELISA	FIV ELISA	FIV FA	FIV WB	Disease	Site of neoplasia
1	–	+	ND	+	MPD	Bone marrow
2	+	+	ND	+	MPD	Bone marrow
3	+	+	ND	ND	MPD	Bone marrow
4	+	+	ND	ND	MPD	Bone marrow
5	+	+	ND	ND	MPD	Bone marrow
6	–	+	ND	ND	LSA	Mandibular lymph node
7	–	+	ND	+	LSA	Mesenteric lymph node
8	–	+	ND	ND	LSA	Kidneys
9	–	+	ND	ND	LSA	Liver
10	–	+	+	+	LSA	Periorbital area
11	–	+	ND	ND	LSA; SCC	Diffuse; nasal plarum
12	–	+	ND	ND	SCC	Sublingual
13	–	+	ND	ND	SCC	Sublingual
14	–	+	ND	+	SCC	Mandible
15	–	+	ND	ND	SCC	Mandible
16	–	+	ND	+	SCC	Nasal planum
17	–	+	ND	+	SCC	Nasal planum
18	–	+	ND	+	SCC	Nasal planum

FA = Fluorescent antibody; WB = western blot; ND = not done; + = positive and – = negative result.
See Table 1 for key.

Results

Twenty-nine (2.5%) cats had FIV-induced disease; 62% (18/29) had neoplasia as the primary illness. Only 0.8% (6/766) of FIV-infected cats referred to the general practice developed neoplasia (Table 1). The referral-to-general practice patient ratio was 2:1 for cats with FIV-related neoplasia. Combined FeLV/FIV infections were seen in 33% of the FIV-infected cats with neoplasia. (Table 2)

Age of FIV-infected cats corresponded to type of neoplasia. Younger cats (median age, 4 years; range, 8 months to 13 years) were concurrently infected with FeLV and had MPD. Cats with LSA

[a]Feder BM, Hurvitz A. Feline immunodeficiency virus infection in 100 cats and association with lymphoma (abstr) *Proc 8th ACVIM Forum* 1990.

[b]Rideout BA, Lowenstein LJ, Moore PF, et al. Pathology of feline immunodeficiency virus (FIV) and FeLV dual infection in specific pathogen free (SPF) cats (abstr) *Proc ACVP and ASVCP* 1989;229.

[c]Macy DW, Podolski CL, Collins J. Prevalence of FeLV and FIV high risk cats in Northeastern Colorado (abstr) *Proc 10th Ann Vet Can Soc Conf* 1990;38.

[d]CITE FIV antibody test kit or CITE COMBO FeLV antigen/FIV antibody test kit, IDEXX Corporation, Portland, Me.

[e]CITE FeLV antigen test kit, IDEXX Corporation, Portland, Me.

[f]Hansen Veterinary Immunology, Dixon, Calif, and Dr. W. Hardy, Jr, Memorial Sloan Kettering Cancer Center, New York, NY.

[g]Epogen Rx, Am Gen, Thousand Oaks, Calif.

[h]Cytoxan Rx, Bristol-Meyers, Syracuse, NY.

[i]Prednisone Rx, Superpharm Corporation, Central Islip, NY.

[j]Oncovin Rx, Eli Lily Co, Indianapolis, Ind.

[k]Adriamycin Rx, Adria Lab, Dublin, Ohio.

[l]Maxitron 300, General Electric, Milwaukee, WI.

Table 3—Survival times for FIV-infected cats with neoplasia

No. of Cats	Disease, site	TX	Days from FIV diagnosis	Days from disease diagnosis	Cause of death	Outcome
1	MPD, bone marrow	TX	249*	249*	A	A
2	MPD, bone marrow	TX	175	6	DOD	E
3	MPD, bone marrow	TX	286	134	DOD	E
4	MPD, bone marrow	NO	2	2	DOD	E
5	MPD, bone marrow	TX	21	21	DOD	E
6	LSA, mandibular node	TX	45	45	DOD	E
7	LSA, mesenteric node	TX	39	39	DOD	E
8	LSA, kidneys	TX	217	217	DOD	E
9	LSA, liver	NO	126	59	DOD	E
10	LSA, periorbital area	TX	243	243	DOD	D
11	LSA, diffuse; SCC, nasal planum	NO	60	60	DOD	E
12	SCC, sublingual	NO	630	1	DOD	E
13	SCC, sublingual	NO	28	27	DOD	E
14	SCC, mandible	TX	247	247	DOD	E
15	SCC, mandible	TX	427	427	DOD	E
16	SCC, nasal planum	TX	+27	+27	A	A
17	SCC, nasal planum, eyelids	TX	+27	+27	A	A
18	SCC, nasal planum	NO	+1	+1	A	A

*Still alive.
NO = no anti-neoplastic treatment given; TX = anti-neoplastic treatment. (*See* text); DOD = dead of disease; E = euthanatized; D = died; A = alive.

Table 4—Reactive lymphadenopathy in ten FIV-infected cats*

Cat No.	Findings	Site
1	LSA; reactive lymphadenopathy	Right submandibular node; left submandibular node
2	LSA; reactive lymphadenopathy	Periorbital area; submandibular lymph node
3	LSA; SCC; reactive lymphadenopathy	Diffuse; heart, kidneys; nasal planum; submandibular lymph node
4	LSA; reactive lymphadenopathy	Mesenteric lymph node; inguinal lymph node
5	Reactive lymphadenopathy hyperglobulinemia	Peripheral lymph nodes
6	Reactive lymphadenopathy febrile	Submandibular lymph node
7	Reactive lymphadenopathy, anemia, antiglobulin positive), dermatitis	Axillary lymph node
8	MPD; reactive lymphadenopathy	Bone marrow; submandibular lymph node
9	MPD; reactive lymphadenopathy	Bone marrow; submandibular lymph node
10	SCC; reactive lymphadenopathy; demodicosis	Left mandible; left submandibular lymph node; left mandible

*Lymphadenopathy in FIV-infected cats is frequently hyperplastic and may exist concurrently with neoplasia.

tended to be mature adults or older (median age, 8 years; range, 4 to 14 years). Geriatric cats (median age, 12 years; range, 7 to 16 years) developed SCC. The male-to-female ratio was 1.6:1; 73% (8/11) of the males were neutered. Breed predilection was domestic shorthair; only 17% of the cats were exotic breeds.

Three neoplastic diseases were observed: MPD (5/18), LSA (5/18), and SCC (7/18). One cat had LSA and SCC. The sites of LSA were submandibular and mesenteric lymph nodes, liver, kidneys, periorbital area, and diffuse sites. In cat 11, the diffuse sites were heart, peritracheal blood vessels, pancreas, kidneys, urinary bladder, and brain. Sites of SCC (Table 2) were sublingual (n = 2 cats), nasal planum (n = 3 cats), nasal planum and eyelids (n = 1 cat), and mandible (n = 2 cats). Survival time (Table 3) for the neoplastic processes varied with response to treatment and site of disease. Survival time for MPD was short (2, 6, 21, 134, and 249 days). Survival time for LSA was 39, 45, 217, and 243 days for treated cats and 59 and 60 days for nontreated cats. Survival time for SCC varied by site: sublingual, 1 and 27 days; mandibular, 247 and 427 days. Three cats with cutaneous SCC were recently diagnosed with the disease and are still alive.

Survival time ranged from 1 day to 427 days and in all but cat 12, it corresponded to the time of evaluation for the neoplastic process and for FIV. (Table 3) The longest FIV infection duration was 1.7 years for cat 12. Although FIV-infected cats may be healthy for prolonged periods, cat 12 was consistently ill with vomiting, diarrhea, upper respiratory tract infections, severe pruritis, and finally lymphadenopathy prior to developing sublingual SCC.

Lymphadenopathy in 10 FIV-infected cats was suspected to be LSA, but was diagnosed histologically as lymphocytic-plasmacytic or reactive lymphadenopathy (Table 4). Reactive lymphadenopathy was identified in 4 cats with extra-nodal LSA and in 2 cats with MPD, and 1 cat with SCC.

Discussion

In our study, 62% (18/29) of the FIV-infected cats had neoplasia. In previous reports of FIV-infected cats, neoplasia ranged from 1 to 21%.[4-9,a,b] Sampling bias toward cats of the oncology referral service was intentional and would explain the high percentage of FIV-related malignancies. However, 33% of the cats with neoplasia were from the general practice.

Surprisingly, only 3 types of neoplasia were

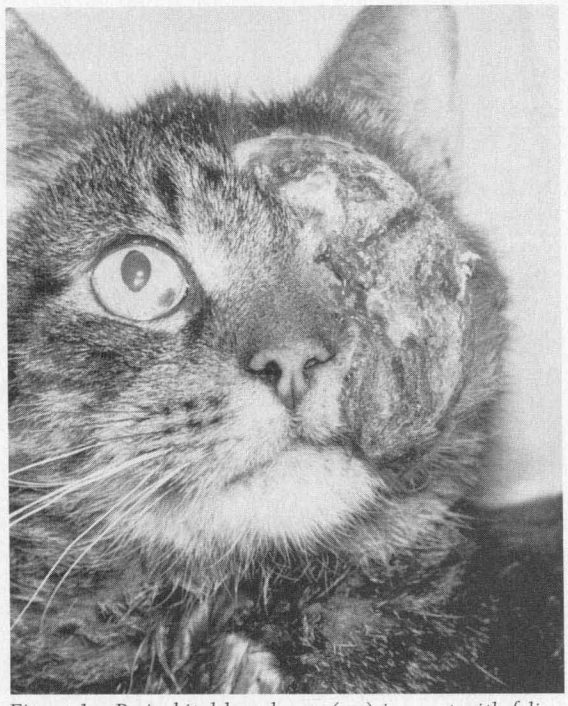

Figure 1—Periorbital lymphoma (LSA) in a cat with feline immunodeficiency virus (FIV) infection. Periorbital and adnexal infiltration prevented visualization of left eye. This unusual site has been recorded twice in association with FIV. Extranodal sites of LSA are frequently observed in FIV-infected cats.

represented. Twelve cases of unusual FIV-related neoplastic disease have been documented in veterinary literature. These tumors may represent ancedotal findings or markers of immune suppression caused by FIV. Our study's 18 FIV/neoplasia may be too small a sample size to elucidate other FIV related neoplasms. Cats infected with FIV appear to have a higher incidence of LSA and MPD.[4,a] Shelton et al[4] found that the relative risks for developing leukemia/lymphoma were 5.6, 62.1, and 77.3 times greater in cats infected with FIV, FeLV, or FeLV/FIV, respectively. Feder and Hurvitz found that 21% of FIV-infected cats suffered from LSA. Sabine et al[7] found that 3/14 Australian cats with LSA were FIV infected (2 with FIV alone; 1 with FeLV and FIV). Of 44 cats with experimentally induced lymphoma in the same study,[7] 9 (20%) were also FIV infected. In a report by Zenger,[6] 8% of FIV-infected cats had neoplasia.

Results of our study supported previous findings that lymphoid tumors in FIV-infected cats developed more frequently in cats >6 years old, more frequently in males than females, and were commonly solitary in nature.[4,a] The signalment pattern for FIV-infected cats with LSA is different than that for cats with FeLV-induced lymphoma, which tends to develop almost equally in either gender and more often in cats between 1 and 5 years old.[10] Numerous reports document neoplasia in association with FeLV and FIV or with FIV infections alone.[4-9,11-20,a,b] The older age of FIV–infected cats may correlate to a long course of antigenic stimulation of the B cells prior to development of lymphoma.

In people with HIV infection, the incidence of LSA increases with time. Three years from HIV diagnosis, 46% of patients will have developed lymphoma.[21] In our FIV study, serologic diagnosis was detained in association with evaluation for neoplasia. Therefore, the interval from time of initial FIV infection to detection of LSA was not determined. A short time course from experimentally induced FIV infection to onset of MPD was documented by a study to be approximately 2 months.[9] Lymphoma and MPD observed in cats with experimentally induced FeLV/FIV co-infection were diagnosed between 16 and 20 months after FIV infection.[b] It is apparent that time is not the singular variable which increases development of disease, but that other oncogenic viruses or diseases may synergistically accelerate development of neoplasia.

Extra-nodal, (bizarre) LSA appear to be more common in FIV-infected cats reported in the literature as well as those (4/6; 67%) of this study. An extremely uncommon LSA site, periorbital lymphoma (Fig 1), has now been documented in 2 FIV/FeLV-infected cats.[6] Head and neck LSA were reported in 5 of 21 cats (2 laryngeal, 2 sinonasal, 1 oral, and 1 nictitating membrane sites).[a] In 2 other studies,[13,18] head and neck LSA were described. In 21 FIV-infected cats with LSA, the gastrointestinal tract or kidneys were involved.[a] Results of our study concurred with those of previous FIV studies correlating solitary, extra-nodal LSA arising from possible sites of pre-existing, plasmacytic-lymphocytic inflammation (ie, intestine or oral cavity). Similarities in FIV- and the HIV-related LSA were: unusual age population, extranodal sites, and high incidence of LSA in general. Similar to FIV, unusual tumors associated with HIV have been documented and may be anecdotal.

Myeloproliferative disease has been diagnosed in some FeLV-negative/FIV-positive cats that have severe anemia and leukopenia.[5,6,9,12] An MPD was experimentally induced by administration of FIV only in a specific-pathogen-free cat, indicating that FIV may be directly oncogenic.[9,22] In our study, all cats with MPD had FeLV/FIV infection, indicating possible oncogeneic synergism.

The synergism of FeLV and FIV infections has been addressed.[23,b] In our study, 28% (5/18) of cats with FIV-related neoplasia were also infected with FeLV. Other reports have indicated concurrent infections to be 15 to 30%.[4,5,7,24-26] Shelton et al[4] confirmed strong association between FeLV infection and LSA and an even greater risk of LSA in cats infected with FeLV and FIV (77-fold increased risk). The same authors[4] observed 2 cats with fibrosarcoma that were infected with FeLV, FIV, and feline sarcoma virus.

In a study of the CT600 strain of FeLV (subgroup A) and FIV, viral synergism has been found to

cause tumors. The CT600 strain was inoculated in more than 200 cats; LSA or MPD was not induced in any cat. However, when a group 10 CT600 FeLV-infected carrier cats (not manifesting signs of disease) were coinfected with FIV, half of the cats died acutely and the remainder survived the acute stage. One of the survivors developed alimentary LSA and another was euthanatized when MPD developed 20 months after FIV–induced infection and 9 months after inoculation with *Haemobartonella felis*.[m] It is possible that FIV and *Haemobartonella* infections act as co-carcinogens to disturb the immune system, most likely by chronic antigen stimulation and B-cell proliferation at a time when cellular DNA is heavily integrated with FeLV CT600 provirus. It is logical to assume that the immunosuppression caused by FIV in cats would predispose them to various neoplasms.

Forty-seven percent of the cats with FIV-related neoplasia had SCC. Oral SCC has previously been reported by Macy et al[c] to have higher incidence in FIV-infected cats. However, owing to lack of controls, we could not conclude that the incidence of SCC was higher in FIV-infected vs noninfected geriatric, nonwhite cats in Southern California.

Treatment efficacy for FIV-induced malignancy remains to be determined; this study was too small for the data to be significant. Survival time for the human counterparts (HIV-induced non-Hodgkins and Hodgkins LSA) have been documented to be short (4- and 15-month median, respectively).[27] Less aggressive chemotherapy regimens and decreasing the dose of cyclophosphamide have been suggested by Kaplan et al[28] to minimize immune suppression in people with HIV-related LSA. Partial response of 2 of our FIV-infected cats with LSA is indication of chemotherapy efficacy. Response to treatment in FIV-infected cats with SCC was not different from that in historical controls.[n]

Lymphadenopathy associated with FIV infection can be markedly severe as in 10 of the cats of this study. Lymphadenopathy in 3 FIV-infected cats with extranodal LSA was determined to be lymphocytic-plasmacytic proliferation and not progressive LSA. Therefore, diagnosis of LSA does not rule-out concurrent FIV-induced lymphadenopathy and vice versa. Cytologic or histopathologic findings will assist the clinician in differentiating between LSA treatment failure and LSA remission in cats with FIV-induced lymph node hyperplasia. Pathognomonic lymph node histologic features have not been determined for FIV infection or for FIV-related LSA.[20,o]

In conclusion, many similarities exist between FIV- and HIV-related malignancies: abnormal older age group with LSA, high incidence of LSA, extranodal LSA site, and synergism with oncogenic viruses. These similarities indicate the usefulness of the FIV animal model for studying the relationship of lentiviruses and neoplasia.

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Comparison of diagnostic methods for feline leukemia virus and feline immunodeficiency virus

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It is important that diagnostic tests for the feline retroviruses, FeLV and feline immunodeficiency virus (FIV), be as accurate as possible. This is especially true for FeLV tests, because in some circumstances, healthy cats found to be seropositive may be euthanatized. The development of in-office tests based on ELISA has led to widespread testing of cats. It is important, therefore, that the underlying biology relating to the tests is understood and that possible problems in interpretation of results should not be overlooked.

Tests Available for FeLV Diagnosis

The most widely used sample for FeLV testing is blood. Cats with persistent infection are viremic, and infective virus, free viral antigen, and neutrophils containing viral antigen are in the blood. Consequently, viremia may be detected by virus isolation (VI), detection of plasma antigen by ELISA, or detection by immunofluorescence (IF) of antigen in the cytoplasm of neutrophils on fixed blood smears. Comparison of results using each test indicates that VI and IF give exactly the same result and presumably measure the same biological activity in the cat (ie, growth of virus in the bone marrow).[1]

Differences in Results Between FeLV Tests

Soon after the introduction of the first in-office ELISA, we reported that around 30% of cats that tested positive by ELISA tested negative by VI.[2] Because we considered VI to be a sensitive indicator of FeLV infection, this result was surprising and disconcerting. Subsequently, the commercial ELISA was modified by inclusion of monoclonal antibodies, then was found to give results more in agreement with VI or IF. In a large series of tests, we found that all samples that were negative by ELISA were also negative by VI.[1] However, about 10% of 2,000 blood samples tested in our diagnostic laboratory by ELISA[a] had positive results but still did not yield infective virus (Table 1). In this way, we identified 'discordant' cats. The discordant state was not associated with 1 particular test. We found that 6 commercial tests were in good agreement in identifying positive, negative, or discordant samples.

Table 1—Comparison of ELISA and virus isolation (VI) for detection of FeLV

Total No. of Samples	ELISA-positive samples		
	Total	VI-positive	VI-negative
2,000	280	245 (88%)	35 (12%)

Relevance of Discordant FeLV Results

Positive ELISA results from the blood of these cats were not attributable to artifact, but indicated a situation in which viral antigen was detected in the plasma when infective virus was not. Several reasons have been proposed for this state. One possibility is that the discordant state represents

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[a]Leukassay-F, C-Vet Ltd, Bury St, Edmunds, England.