Feline Preleukemia: An Animal Model of Human Disease [1]

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In man, hematologic abnormalities precede the development of acute myeloblastic leukemia in about one-third of individuals. This preleukemic state may represent a stage of adult leukemia wherein small numbers of leukemic cells are present and the normal marrow stem cell compartment has not been seriously compromised. A syndrome resembling human preleukemia occurs in cats infected with feline leukemia virus (FeLV). This disorder is characterized by anemia, leukopenia or thrombocytopenia occurring weeks or months prior to the development of feline acute leukemia. The natural occurrence of this syndrome in this domestic animal population makes it a potential model of human preleukemia. Initial poor results of therapy of human preleukemia presently prohibit one from carrying out controlled trials with chemotherapeutic agents in such a group of patients. Preliminary trials with chemo- and/or immunotherapy may be more easily attempted with FeLV infected preleukemic cats.

INTRODUCTION

Lymphoid neoplasia is the most commonly occurring malignancy in domestic cats, accounting for at least 1/3 of the malignant tumors in this species [1,2]. One epidemiologic study estimated the incidence of feline lymphoid malignancies as being 200 cases/100,000 cats in the population at risk [3]. This incidence is considerably higher than that of leukemia in man or in other domestic animals. The term "feline leukemia" is used in much of the literature to describe a leukemia-lymphoma complex. In most instances the principal cell type involved is lymphoid in origin but myeloproliferative disorders (myelogenous leukemia, erythroleukemia, monocytic leukemia, and polycythemia vera) have also been described [4-10].

The suggestion that feline leukemia may be caused by a virus was first provided by Jarrett and his co-workers in 1964 [11]. These investigators induced lymphosarcoma in newborn kittens by injecting cell suspensions from a naturally occurring feline mediastinal lymphoma. The kittens developed lymphosarcoma after periods of time ranging from nine to 18 months. Electron microscopic examination of this tumor

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tissue revealed C-type virus-like particles similar to those associated with avian and murine leukemia [11]. It soon became apparent that a contagious and oncogenic feline leukemia virus (FeLV) was responsible for the majority of naturally occurring feline lymphoid malignancies [12–15]. In 1970 a simple immunofluorescent test was developed for the detection of viral group-specific antigens in the leukocytes and platelets of viremic cats [15]. These antigens are present in 70 to 90% of cats with naturally occurring lymphoma and leukemia [16–18]. A positive result by immuno-fluorescence correlates well with virus isolation in tissue culture [15]. FeLV also has an effect on non-hematopoietic tissues. Investigators have observed thymic atrophy, lymphoid depletion and an apparent increased susceptibility to infection in cats inoculated with FeLV [18,19]. The viremic, potentially leukemic cat has been shown to have an altered cell mediated immune response and perhaps an altered humoral response as well. Other diseases have been associated with FeLV infection including feline infectious peritonitis, glomerulonephritis, spontaneous abortion, fetal resorp-tion, and nonregenerative anemia [16,20,21].

Two classes of antigens have been described in association with FeLV infected cells: (a) the non-virion viral specific cell surface antigen (Feline Oncornavirus Cell Membrane Antigen, FOCMA) that appears on the surface membrane of FeLV transformed cells, and (b) the virion type specific antigens associated with the viral envelope. The FOCMA antibody titer and neutralizing antibody titer can be measured in viremic cats. The specificity of the FOCMA antibody has been documented experimentally with various strains of feline oncorna viruses [22–24]. Viremic, leukemic cats have low FOCMA and neutralizing antibody titers. FOCMA is not present in normal peripheral blood, bone marrow or lymphoid tissue until these cells are transformed into neoplastic cells and FOCMA is thought to be a tumor specific antigen [25].

Anemia observed in FeLV infected cats may occur coincidentally with the development of a solid lymphosarcoma, and of lymphoid and myeloid leukemia. Nonregenerative anemia in the viremic cat, unassociated with neoplasia, may progress to leukemia. Due to the poor prognosis, cats with hypoplastic anemias are terminated and transition to acute leukemia is rarely seen. In some instances when supportive therapy is administered or when the animal stabilizes spontaneously, a lymphoproliferative or myeloproliferative disorder may evolve. Not all FeLV positive anemic animals progress to leukemia and viremic cats may remain hemato-logically and clinically normal for long periods of time [26]. In a prospective study of 148 clinically normal FeLV positive cats, 7.5% expired with severe anemia while 16.2% developed histologically confirmed lymphosarcoma in a two-year period [27]. As occurs in man, some animals may expire in a preleukemic stage of disease due to the systemic manifestations of anemia.

In man the hematologic abnormalities that precede the development of acute myeloblastic leukemia have recently been categorized into a recognizable syndrome that may be appropriately labeled "preleukemia" [28–31]. Although once thought to be a rare occurrence, an initial preleukemic phase was documented in 1/3 of individuals in a study of 132 patients with acute non-lymphocytic leukemia [29]. On the other hand, a preleukemic syndrome has been described only rarely as a harbinger of the acute lymphoblastic leukemia of childhood [32]. This entity is attracting increased interest and multiple authors have different definitions of a criteria for the identification of the preleukemic syndrome. Many believe that the diagnosis of preleukemia can be made only retrospectively. Human preleukemia may represent a stage of adult leukemia where small numbers of leukemic cells are present

and where the normal marrow stem cell compartment has not been seriously compromised in size or function. It has been suggested that the preleukemic state might be an appropriate setting for testing the hypothesis that chemotherapy and/or immunotherapy is most effective when the tumor cell load is small [30]. Initial attempts at aggressive therapy during this phase of disease have proven disastrous and have been discouraged by several investigators [33]. These results make it difficult to undertake controlled trials with chemotherapeutic agents in man. Preliminary studies may be more easily undertaken if an appropriate animal model for the development of the preleukemic state existed.

This paper describes a naturally occurring syndrome in domestic cats that resembles human preleukemia. These animals manifested hematologic abnormalities for variable periods of time prior to the development of overt leukemia. This syndrome appears to be an appropriate model for further investigation of the preleukemic state in man.

CLINICAL DESCRIPTION OF FELINE PRELEUKEMIA

We have had the opportunity to document the clinical course of twelve domestic FeLV+ anemic cats presenting to the University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, the Animal Medical Center, New York, New York, and the Angell Memorial Animal Hospital, Boston, Massachusetts. Each animal presented with unexplained cytopenias and/or refractory anemia prior to the development of overt leukemia (Table 1).

The population included nine males and three females. Ten of the twelve animals were young adults (4 years old or less) with the oldest animal being 13 years old. Animals were referred for evaluation of lethargy, anorexia and weight loss of up to six months duration. Physical findings were remarkable for mucous membrane pallor (8/12), fever (8/12), and hepatosplenomegaly (6/12). Hematological evaluation included determination of complete blood counts, reticulocyte counts, estimated platelet numbers and evaluation of bone marrow aspirations from the dorsal iliac crest.

TABLE 1
Clinical Summary of 12 Cases of Feline Preleukemia

Case No.	Age (yr)	Sex	Interval of Anemia to Leukemia (mos.)	FeLV Status Preleukemic Phase[+]	Leukemia Type
1	1	F	0.5	+	Lymphoblastic
2	8	M	33.0	−	Erythroleukemia
3	3	F	2.0	+	Lymphoblastic
4	1	M	0.25	+	Lymphoblastic
5	2	M	1.25	+	Lymphoblastic
6	3	M	18.0	+	Erythroleukemia
7	1.5	M	2.0	−	Myeloblastic
8	13	M	2.0	+	Lymphoblastic
9	2	M	1.0	+	Lymphoblastic
10	3	M	8.0	+	Lymphoblastic
11	3	M	1.0	+	Lymphoblastic
12	4	F	4.0	+	Lymphoblastic

M, male; F, female.
+ By fixed cell immunofluorescent test [15].

TABLE 2
Initial Hematologic Findings in 12 Cases of Feline Preleukemia

Case No.	Hemato-crit %	Reticu-locytes %	Nucleated RBCs/ 100 WBC	WBC × 10³/ cu mm	Nl	B	L	M	E	Me	Bl	Estimated Platelet Nos.
1	28+	NA	2	33.9	89	2	8	2	2	—	0	N
2	20	1.4	0	2.6	12	—	80	4	4	—	0	N
3	10	0	NA	NA								
4	8	0.1	2	2.1	64	—	36	—	—	—	0	↑
5	7	4.0	0	4.1	64	9	24	—	—	—	3	↑
6	18	NA	445	3.6	9	8	79	2	2	—	0	N
7	15	0	3	3.7	71	1	28	—	—	—	0	↓
8	15	2.0	58	5.2	92	—	7	—	1	—	0	↑
9	19	0	0	2.2	28	4	64	—	—	4	0	↓
10	11	0.3	29	2.9	59	—	41	—	—	—	0	↓
11	16	0	0	1.7	32	50	18	—	1	—	0	↓
12	7	3.2	4	8.1	79	1	19	1	—	—	2	↓

Normal values (35), in mean/cu mm (range/cu mm): PCV, 37% (24–45); WBC, 12,500/cu mm (5,500–19,500); neutrophils, 7,500/cu mm (2,500–12,500); lymphocytes, 4,000/cu mm (1,500–7,000); reticulocytes (0–1%).

NA, not available; ↑, increased; ↓, decreased; N, normal; Nl, neutrophil; B, band; L, lymphocyte; M, monocyte; E, eosinophil; Me, metamyelocyte; Bl, blast.

+ extreme dehydration.

All twelve animals were anemic (mean hematocrit of 14.5%) and the anemia was severe in four animals (Table 2). Although macrocytosis without polychromasia was occasionally evident on the peripheral blood smear, normochromic, normocytic red blood cell (RBC) morphology was the rule. Nucleated RBC precursors, some of which were megaloblastoid, were commonly observed (10/12). Reticulocytosis was noted in three cats at presentation but they later reverted to reticulocytopenia. All other animals presented with depressed reticulocyte counts. The white blood cell (WBC) abnormalities at presentation were confined to leukopenia (mean WBC of 6.4 × 10³/cumm) with granulocytopenia. One animal, however, presented with a wwbc of 33,900/mm³ (Table 2). Atypical lymphocytes and blast forms were present (2 to 9%) in the blood of two of twelve cats during the preleukemic anemic phase. Platelet numbers were variable. Large platelets with bizarre morphology were seen in three cats with thrombocytosis. Bleeding tendencies were not observed. Only two of the twelve cats were FeLV negative when they presented with anemia. These two animals became viremic when they developed overt leukemia.

Bone marrow aspirates were examined during the preleukemic phase of disease in eight cats (Table 3). Cellularity was normal in marrows of four cats, decreased in that of three cats and increased in the aspirate of one cat which later developed myelogenous leukemia. Erythroid hypoplasia with maintenance of other cellular elements was observed in the marrow of three animals while pancytopenia was noted in that of two other cats. Erythroid maturation was megaloblastoid in some instances. Mild to moderate lymphocytosis was noted in four of eight aspirates. Bone marrow aspirates were infiltrated with blast forms in all animals when overt leukemia was diagnosed. As noted in Table 1, blasts were most often lymphoid in morphology (9/12), although the marrow findings of both erythroleukemia and myelogenous leukemia were also observed.

The interval of time from the development of anemia to the diagnosis of overt

TABLE 3
Initial Bone Marrow Findings in 8 Cases of Feline Preleukemia[+]

Case No.	Cellularity	Erythroid Elements	% Blasts	Megakaryocytes	Lymphocytes
3	↑	↑	NA	↑	↑
4	N	↑	3	N	N
5	N	↑	0	↑	N
7	↑	↑	4	N	N
8	N	↑	3	↑	↑
9	↑	↑	1	N	↑
10	N	↑	6	↑	↑
11	↑	N	0	N	↑

N, normal; ↓ increased; ↑ decreased; NA, not available.
[+]Cases 1, 2, 6, and 12 did not have bone marrow aspirates during preleukemic phase.

leukemia varied from one week to 33 months (Table 1). During this period, all animals were given some form of therapy. Blood transfusions (cases 2, 3, 4, 5, 8, 10, 12), anabolic steroids (cases 3, 8, 9, 10, 12), corticosteroids (cases 5, 8, 10, 11), and intralymphatic BCG (case 8) were administered. Following the diagnosis of overt leukemia, animals were most often sacrificed at the request of their owners. The remaining few, in which therapy was attempted, died two to three weeks later.

Necropsies were performed on nine animals and blast cell invasion of bone marrow, liver and spleen was noted. In addition, neoplastic involvement of the kidney (cases 10, 12), lymph nodes (cases 6, 10, 11), heart (case 10), and eye (case 10) was recorded.

DISCUSSION

Observations to date leave little doubt as to the existence of a recognizable hematologic syndrome preceding the development of acute nonlymphocytic leukemia in man [28–31]. This syndrome has been designated the "preleukemic syndrome" and is not a separate entity or a specific disease but is rather a stage in a multiphasic leukemic disorder. The duration of preleukemia is variable and it is likely that this reflects differences in host responses rather than different pathogenic mechanisms.

We report a preleukemic disorder in FeLV positive cats that resembles that described in man. The similarities of feline preleukemia and human "prelymphoblastic" leukemia are evident. Although feline leukemia is most often lymphoid in nature, there is also a striking resemblance between this preleukemic disorder and the syndrome that frequently precedes the development of human acute nonlymphoblastic leukemia. Murine leukemia has been utilized by many investigators as a model for human disease but this occurs in highly inbred, artificially maintained laboratory animals and produces solid tumors rather than a true leukemia. Feline leukemia may be a more appropriate model for human leukemia due to its natural occurrence and its restriction to the bone marrow and lymphoid tissues in a domestic population [34]. The appearance of cytopenias and refractory anemia in feline preleukemia is similar to the situation in man.

Feline leukemia offers the investigator an unusual opportunity to observe a leukemia while its manifestations evolve. Nonregenerative anemia has been experimentally produced in young kittens inoculated with the Kawakami-Theilen (KT) strain of feline leukemia virus [35,36]. It is possible that if supported through their

anemic phase, many of these animals may develop lymphosarcoma or some form of leukemia. Serological studies allow identification of FeLV + animals with a high risk of developing acute leukemia. Extensive studies have been performed on the immunological response to FeLV infection [37–39]. Exposure of cats to FeLV results in the expression of FOCMA after contact exposure to virus under laboratory and field conditions [22]. The levels of FOCMA antibody have been shown to be predictive for tumor occurrence and growth. Animals with high FOCMA antibody titers are less likely to develop tumors [23,35,38]. The humoral response to FOCMA may function as an immunosurveillance mechanism and may prevent the development of leukemia following infection with FeLV under natural conditions.

The accumulation of evidence for a dominant role of cellular immune mechanisms in tumor rejection [40,41] and the observation that humoral antibodies may enhance rather than inhibit tumor growth [42,43] have led to the premature dismissal of the therapeutic role of antibodies directed against tumor associated antigens expressed on tumor cells. The effect of antiserum treatment on the growth of allogenic tumors has been extensively investigated [42,43]. Both active and passive immunization resulted in either enhancement or inhibition of tumor growth, depending upon the conditions of the immunization. Sporadic reports suggesting the potential benefit of serotherapy in the treatment of human malignancy have been published but remain unsubstantiated [44–46]. Such studies in man may be premature pending the isolation of a truly tumor-specific antigen. The feline preleukemic state may be an ideal situation in which to test the effect of serotherapy on a naturally occurring tumor. FOCMA is a well defined tumor specific antigen and the levels of FOCMA antibody are associated with protection against tumor development [22]. The administration of FOCMA antibody rich serum to cats with preleukemia may allow for the observation of the effect of serotherapy on animals with a relatively low tumor burden. It would be important to know whether or not such therapy may be combined with chemotherapy or immunotherapy to stimulate cell mediated immunity.

The role of intensive chemotherapy in human preleukemia is unknown. Anecdotal reports have suggested that such intervention has met with disaster [33]. Studies designed to test a variety of agents in feline preleukemia would allow the chemotherapist the opportunity to alter the course of naturally occurring preleukemia. At present similar studies in man are unethical insofar as preleukemic individuals may survive long periods of time with supportive care alone.

This report describes a feline preleukemic syndrome that closely resembles human preleukemia. This animal model of human disease will hopefully be useful to virologists, tumor biologists, and experimental chemotherapists.

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