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Diseases Associated with Spontaneous Feline Leukemia Virus (FeLV) Infection in Cats

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ABSTRACT

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More than 2000 cats sent for necropsy in order to provide a diagnosis were investigated immunohistologically using paraffin sections for the presence of a persistent infection with feline leukemia virus (FeLV). The spectrum of neoplastic and non-neoplastic diseases associated significantly with FeLV infection was determined statistically. Three-quarters of the cats with persistent FeLV infections died of non-neoplastic diseases and about 23% died of tumors, nearly exclusively those of the leukemia/lymphoma disease complex. A strong association with liver degeneration, icterus and a FeLV-associated enteritis was found in addition to the known association with non-neoplastic diseases and conditions such as anemia, bacterial secondary infections and respiratory tract inflammations due to the immunosuppressive effect of FeLV, hemorrhages and feline infectious peritonitis. Surprisingly, diseases and conditions like feline infectious panleukopenia, enteritis (of other types than FeLV-associated enteritis and feline infectious panleukopenia), glomerulonephritis, uremia and hemorrhagic cystitis were not associated with persistent FeLV infection. Another unexpected finding was that most pathogenic infectious agents demonstrated in the cats were not FeLV-associated either. Thus, immunosuppression due to FeLV infection seems to make the animals susceptible to certain pathogenic infectious agents, but not to the majority.

INTRODUCTION

Persistent infection of cats with FeLV is associated with a wide spectrum of non-neoplastic diseases and with some tumors, of which only those of the leukemia/lymphoma complex and fibrosarcomas are generally accepted to be induced by or associated with FeLV infection. However, there has been comparatively little study of how often FeLV induces which disease, and how stringent is the association between a given disease and spontaneous FeLV infection. We therefore studied the frequency of FeLV infection in a large population of cats

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sent for post-mortem examination and determined the association of diseases and conditions of these cats with FeLV infection.

MATERIAL AND METHODS

A total of 2069 cats sent for necropsy to the Department of Veterinary Pathology, University of Giessen, West Germany, were investigated immunohistologically from 1980 to 1988 for persistent FeLV infection. The results from 1095 cats were studied statistically (Chi square, Fisher's and Kruskal-Wallis test) for significant association between diseases and conditions of the animals and FeLV infection. The control population for these statistical tests consisted of cats killed by trauma, a cause of death presumptively not FeLV-associated.

The immunohistological examination of tissues fixed in methanol and embedded in paraffin was done as published previously (Reinacher and Theilen, 1987). Briefly, endogenous peroxidase was blocked by incubation for 30 min in methanol containing 0.5% H_2O_2. An indirect immunoperoxidase method was performed with polyclonal or monoclonal antibodies against the FeLV proteins p27 and gp70. Peroxidase activity bound to the tissues was visualized with diaminobenzidine.

RESULTS AND DISCUSSION

Post-mortem diagnosis of FeLV infection

The immunohistological diagnosis of persistent FeLV infection in cats sent for post-mortem diagnosis is a very reliable technique. Neither deterioration of the corpses nor time span between death and post-mortem examination seem to be of importance for the outcome of the test, at least not within the normal range for these factors in our material, where post-mortem examination usually takes place 1 to 5 days after death. The results of immunohistological investigation after death and demonstration of FeLV infection in blood smears in vivo are identical. In one case, FeLV infection was detected immunohistologically even 20 days after death in a cat in the state of advanced putrefaction and autolysis. Freezing of corpses also does not alter the outcome of the test. Immunohistological investigation of bone marrow and spleen are sufficient to detect persistent FeLV infection in more than 99.9% of the FeLV-infected cats.

Frequency of FeLV infection in necropsied cats

The frequency of cats with persistent FeLV infection in the population sent to our department for necropsy was 16%. In comparison, only 3% of the cats killed by trauma (mostly car accidents, gun shots and biting by dogs) — which

represent in a necropsy population the best subpopulation for conclusions about the "normal cat" population — were FeLV positive. This difference in the frequency of FeLV infection in the two populations is highly significant and stresses the pathogenic importance of FeLV infection in cats. The figure of 16% FeLV infection indicates that FeLV is the most frequent cause of a lethal infectious disease in cats. It occurred twice as often as feline infectious panleukopenia and was even more abundant than feline infectious peritonitis which was present in about 14% of the cats sent to our department for necropsy. Only about 20% of the persistent FeLV infections diagnosed in our series of animals have been diagnosed in vivo by practitioners or clinicians. Thus, 80% of these cats with the most abundant lethal infectious diseases have not been recognized with certainty in vivo, although methods to raise this diagnosis are easily available.

Frequency of tumors and non-neoplastic diseases in FeLV-positive cats

Of the FeLV-positive cats, 77% died of non-neoplastic FeLV-associated diseases and only 23% suffered from tumors. Ninety-six percent of the tumors in these cats belonged to the leukemia/lymphoma disease complex and only 4% were of different histogenetic origin. This confirms the epidemiological data of other groups (Francis et al., 1979a) that non-neoplastic FeLV-associated diseases are much more important and frequent consequences of FeLV infection than hematopoietic neoplasms or fibrosarcomas.

Diagnoses and conditions present in more than 5% of FeLV-infected cats

All diagnoses and conditions found in more than 5% of FeLV-infected cats were significantly associated with FeLV infection.

Anemia. The diagnosis raised most often in FeLV-positive cats was anemia. Forty-five percent of the FeLV-infected cats had anemia at necropsy. When anemia was diagnosed at all, 31% of these cats were FeLV-infected. Severity of anemia was established by subjective classification by the pathologist on duty of animals at necropsy in a group suffering from severe anemia — which was regarded as possible cause of death — and a group suffering from milder anemia — which was regarded as not sufficiently severe to explain death of the cat. The percentage of cats with persistent FeLV infection rose to 52% in animals with severe anemia of otherwise unknown etiology — which means exclusion of cats with conditions and diseases such as tumors, hemorrhagic disorders, traumata, infestation with parasites, etc. — whereas only 23% of animals with mild anemia of otherwise unknown etiology were infected by FeLV.

Tumors. The second most frequent lesions in FeLV-positive cats were tumors

of the leukemia/lymphoma disease complex. These neoplasias were present in 23% of the cats with persistent FeLV infection. Differentiation of leukemia/lymphomas at the cellular level (Facklam and Kociba, 1986) revealed that all myeloid and 67% of the undifferentiated leukemias/lymphomas occurred in cats with FeLV infection. Special forms like myelosklerosis and panmyelosis including megakaryocytic leukemia (Juchem and Pause, 1987) tended also to be FeLV positive (83%). Lymphatic leukemias/lymphomas, however, differed to a great extent in their association with FeLV, depending on their macroscopical distribution pattern. All thymic lymphomas were lymphatic and 92% of them developed in FeLV-positive cats. In contrast, 78% of the lymphatic intestinal lymphomas occurred in FeLV-negative animals. The lymphatic multicentric and unclassified (Cotter et al., 1975) leukemias/lymphomas were between these two extremes, 73% and 62%, respectively, occurring in FeLV-infected animals.

The following tumors were also associated statistically significantly with FeLV infection in our material: fibrosarcoma, meningioma, osteosarcoma, squamous cell carcinoma. The number of cases, however, is still too low to give any idea about the stringency of the association between persistent FeLV infection and occurrence of these tumors.

Feline infectious peritonitis (FIP). Lesions typical for infectious peritonitis (FIP) were found in 22% of FeLV-positive cats. Of all cats which suffered from FIP, 19% were infected with FeLV. Significant differences in the association with FeLV between parenchymal and exudative forms of FIP were not demonstrable. FIP is a frequent disease in FeLV-infected cats mainly because FIP is frequent in the cat population as is FeLV. However, 19% FeLV infection in cats with FIP is not significantly above the percentage of FeLV infection in our total necropsy cat population which is 16%. Thus, the stringency of the association between FeLV and FIP is not above the average of all diseases associated with FeLV. The percentage of FeLV infection in cats suffering from FIP in our material (about 19%) was lower than that reported by others (Hardy and Hurvitz, 1971; Cotter et al., 1975; Essex et al., 1975; Weijer and Daams, 1976; Essex, 1982). This may be due to differences in the epidemiological patterns of the two diseases — as a consequence of time or local differences — or to the fact that most of the earlier studies investigated more selected populations and were, therefore, probably biased.

Liver degeneration. Liver degeneration such as liver cell dissociation, fatty liver, focal liver necrosis and liver cirrhosis occurred in 15% of cats with FeLV infection. About 30% to 40% of all cats suffering from these liver disorders were infected with FeLV. Icterus was found in 8% of FeLV-infected cats and 25% of all cats with icterus were FeLV positive. This is the first time a significant association between liver degeneration and FeLV has been found. The patho-

genesis of these liver degenerations is not clear at the moment. FeLV-associated anemia may support some of them, but it is probably not the only, and not even the main, cause of the liver lesions since they also occur in cats without anemia.

FeLV-associated enteritis. A FeLV-associated enteritis (Reinacher, 1987) was diagnosed in 12% of FeLV-positive cats. This enteritis partially resembles feline infectious panleukopenia but it occurs in older animals of mean age 2.5 years — compared to the mean age of 0.5 years of cats with feline infectious panleukopenia — and the course of the disease is subacute to chronic. No parvovirus infection could be shown in these animals by virological methods. Intestinal alterations of cats suffering from FeLV-associated enteritis resemble histologically those of feline infectious panleukopenia since crypt epithelium degeneration, crypt dilatation, vanishing of crypts and villous atrophy are also present. In bone marrow and lymphoid tissues, however, the typical lesions of feline infectious panleukopenia are absent. In contrast, these tissues are unaltered or even hyperplastic with blast proliferation. Of all cats with this type of enteritis, 72% were infected with FeLV. The animals with FeLV-associated enteritis show immunohistologically FeLV protein synthesis in the crypt epithelium of the small intestine. Since FeLV, however, is not cytopathogenic by itself, there might be a second pathogenic mechanism associated with this disease. First immunohistological data indicate that the percentage of intestinal corona virus infection in cats with FeLV-associated enteritis is higher than in cats with other types of enteritis.

Neurological signs in case histories. In 11% of case histories of FeLV-positive cats neurological signs were mentioned. In none of these cats could any positive signals be found immunohistologically in the central or peripheral nervous system. Thus, the pathogenesis of the neurological signs present in FeLV-infected cats is still uncertain. In part they may be explained by the emaciation found in 14% of FeLV-positive cats, but weakness and bodily deterioration alone are not sufficient to explain all the cases and symptoms. About 23% of cats with neurological signs mentioned in the case history were FeLV-infected.

Inflammations of the respiratory tract. Inflammations of the respiratory tract like rhinitis, feline coryza, pneumonia or pleuritis (FIP excluded) were found in 10% of cats with persistent FeLV infection. The percentage of FeLV infection in animals with these inflammations of the respiratory tract varied between about 20% and 30%.

Lymphatic hyperplasia. Lymphatic hyperplasia — either in multiple lymph nodes or in spleen or in both — was present in 8% of FeLV-infected animals,

and 52% of the cats with lymphatic hyperplasia suffered from a persistent infection with FeLV.

Bacterial infections. In 6% of the FeLV-positive cats an infection with pathogenic bacteria was demonstrated by microbiological methods. Pathogenic bacteria associated significantly with FeLV infection were β-hemolytic streptococci (33% FeLV-positive), *Pasteurella* (27% FeLV-positive) and *Salmonella* (33% FeLV-positive).

Hemorrhages. Hemorrhages were found in 5% of FeLV-infected cats. They were mostly general hemorrhagic diathesis (23% FeLV-positive), intestinal hemorrhages (22% FeLV-positive) and brain hemorrhages (29% FeLV-positive).

Diseases and conditions with a significantly higher association with FeLV infection than FeLV infection occurs in the necropsy cat population

When the total necropsy cat population is used as control group for statistical investigation instead of the trauma group, only the diseases and conditions with the strongest association with FeLV will be found as significantly FeLV-associated, which in this context means that FeLV viremia was significantly more frequent in cats with the given condition or disease than FeLV infection occurred in the total necropsy cat population, which itself had 16% FeLV-positive cats. Under these premises the following diseases and conditions were extracted statistically: anemia, the diseases of the leukemia/lymphoma complex with the exception of the intestinal forms, infection with β-hemolytic streptococci, FeLV-associated enteritis, focal myocardial necrosis, icterus, fatty liver, focal liver necrosis and lymphatic hyperplasia. It is obvious that a variety of these alterations are degenerative in tissues other than lymphoid and hematopoietic tissues and thus cannot be explained by immunosuppressive effects of the virus alone. Surprisingly, liver degenerations and icterus, not known to be FeLV-associated until this study was done, show up even in this very high association group.

Association of FeLV with other infectious agents

Often a general susceptibility to secondary infections is claimed for cats with persistent FeLV infection. This phenomenon is thought to be due to the immunosuppressive effect of FeLV (Cotter et al., 1975; Hardy, 1982; Rojko and Olsen, 1984; Theilen and Madewell, 1987). In our material, however, the association between FeLV infection and other infectious agents is rather selective, with no indication of a generally higher susceptibility to all kinds of in-

fectious agents. Thus, none of the mycotic infections occurred in FeLV-positive animals.

Of all viral infections diagnosed by morphological and/or microbiological methods, only FIP was significantly associated with FeLV infection. No significant association was found for pseudorabies virus, feline parvovirus, feline herpesvirus 1 and feline calicivirus. The lack of significance in the association of feline herpesvirus 1 and feline calicivirus is astonishing since, as already mentioned, feline coryza (feline upper respiratory tract disease) and rhinitis were significantly FeLV associated. Seemingly, FeLV infection alone may lead to coryza or rhinitis, or agents other than feline herpesvirus 1 or calicivirus (not tested for in our studies) may be responsible for most of the nasal and upper respiratory tract conditions as a result of immunosuppression from FeLV infection.

Of parasites, only flea infestation had a significant association with FeLV infection; ascarids, aelurostrongylus, ancylostoma, tape worms, coccidia and mites had not. For the coccidia, an association with FeLV infection might exist (33% of the cases were FeLV positive) but the number of cases is still too low to prove that statistically. Whether the association of flea infestation with FeLV infection indicates that fleas transfer FeLV, which seems possible, although unlikely (Francis et al., 1977; Bech-Nielsen et al., 1978; Essex, 1982; Buxton et al., 1985), remains unresolved. The significance could be the result of environmental conditions, whereby propagation of fleas and transmission of FeLV occur together.

The bacteria associated significantly with FeLV infection have already been mentioned above.

Negative association of diseases and conditions with FeLV

Significantly negative association of a disease or condition with FeLV infection could not be demonstrated using the trauma population (3.2% FeLV positive) as control. However, to prove such a negative association statistically, substantially more cats would be needed. For instance, a possible negative association existed with feline infectious panleukopenia, where only 1.6% of cases were FeLV positive. To show a significant negative association when the trauma group was used as control, about 2400 cats infected with feline panleukopenia virus and about 1200 cats killed by trauma would be needed, providing the percentages of 1.6% and 3.2% FeLV infection rate in cats for each category remained constant. It is not feasible to collect such a large group of cats in a reasonable time at one department. Therefore, we searched for diseases and conditions that were significantly less often associated with FeLV infection than was the prevalence of FeLV infection in cats in our necropsy population (16.2% FeLV positive).

Compared with this group of cats, the following diseases and conditions were negatively associated with FeLV infection:
Hemorrhagic cystitis. So far no cat with hemorrhagic cystitis sent to our department for diagnosis was infected with FeLV.
Feline infectious panleukopenia. Only 1.6% of cats with feline infectious panleukopenia, diagnosed histologically and/or virologically, were FeLV-infected.
Unknown cause of death. Only 2.8% of cats with totally unknown cause of death — which means that neither macroscopical investigation nor histological, microbiological, parasitological or toxicological investigation gave results indicating a possible cause of death — were FeLV-infected. This percentage is nearly identical to that of the trauma population (3.2% FeLV positive) and may thus indicate also the percentage of a mere coincidence between FeLV infection and a diagnosis. On the other hand, a lethal FeLV infection is usually accompanied by alterations recognizable by the pathologist.
Primary cardiomyopathy. In 5.3% of the cats with primary cardiomyopathy a FeLV infection was found. This percentage is also significantly lower than the frequency of FeLV infections in the cat population sent for necropsy.
Uremia. The percentage of cats with persistent FeLV infection suffering from uremia is also significantly lower than in the necropsy population and is also 5.3%. This is astonishing since glomerulonephritis has often been mentioned as a typical non-neoplastic FeLV-associated disease. In our material none of the diagnosed glomerulonephritis cases were FeLV positive. When FeLV antigen could be demonstrated immunohistologically in the glomeruli it was always in very tiny amounts not sufficient to suggest any clinical or pathological significance. These glomeruli did not exhibit any histological changes supporting the diagnosis of glomerulonephritis and the animals had no clinical diagnosis of glomerulonephritis, nephritis or renal insufficiency. Thus, glomerulonephritis seems not to be a frequent and important consequence of FeLV infection under natural conditions.
Enteritis. When all other types of enteritis than feline infectious panleukopenia and FeLV-associated enteritis were put together in one group for statistical comparison with the necropsy cat population, a significant negative association with FeLV infection could be shown for these other types of enteritis. Only 6.3% of cats with enteritis were FeLV positive when feline infectious panleukopenia and FeLV-associated enteritis were excluded.

Differences in age between FeLV-positive and FeLV-negative cats

Abortion and fading kitten disease are often mentioned as FeLV-associated conditions (Anderson et al., 1971; Perryman et al., 1972; Hoover et al., 1976; Jarrett et al., 1984). None of the aborted kittens and hardly any kittens younger than 12 weeks of age were FeLV positive, however, in our study. Only 2% of the kittens younger than 12 weeks of age were persistently FeLV infected

whereas 20% of those older than 12 weeks of age suffered from FeLV viremia. This difference in the frequency of FeLV infection between the two age groups is highly significant and it indicates that FeLV infection is not an important disease in newborn and young cats.

FeLV-positive cats are often younger than FeLV-negative cats with the same diagnosis (Gardner et al., 1974; Francis et al., 1979b; Rojko and Olsen, 1984; Theilen and Madewell, 1987). However, this holds true, at least in our study, only for the diseases of the leukemia/lymphoma complex. This group of diseases is the only one in which FeLV-positive cats (mean age 137 weeks) were significantly younger than FeLV-negative animals (mean age 263 weeks). All cats, however, which died of non-neoplastic diseases and suffered from FeLV viremia were significantly older when they were FeLV infected than FeLV-negative cats with the same diagnosis, provided a statistically significant difference in age between FeLV-positive and FeLV-negative cats could be shown at all. This holds true for cats with anemia (mean age of FeLV-positive cats 136 weeks, of FeLV-negative cats 105 weeks), emaciation (mean age of FeLV-positive cats 162 weeks, of FeLV-negative cats 95 weeks), icterus (mean age of FeLV-positive cats 286 weeks, of FeLV-negative cats 187 weeks) and FIP (mean age of FeLV-positive cats 177 weeks, of FeLV-negative cats 94 weeks). Even when not divided into groups according to the condition or disease diagnosed, the FeLV-positive cats in our necropsy population were moderately but significantly older (mean age 157 weeks) than the FeLV-negative cats (mean age 138 weeks). This again supports the interpretation made above that spontaneous FeLV infection is not a disease of young cats but rather of young adult to middle-aged animals.

CONCLUSION

FeLV infection is the most frequent lethal infection of the cat. The spectrum of diseases and conditions associated with spontaneous FeLV infection differs somewhat from that often reported from experimental studies or from investigations performed with a more selected population. One of the reasons for this difference may also be that in our study all cats were necropsied. Thus, some diagnoses not easily raised by clinical investigations could be made or excluded. For instance, glomerulonephritis, feline infectious panleukopenia, hemorrhagic cystitis, abortion and death of young kittens are not FeLV-associated in our cat population. On the other hand, liver degenerations like liver cell dissociation, fatty liver, focal liver necrosis and icterus, which have not been recognized to have any connection with FeLV infection until the present study was done, are significantly FeLV-associated and occur often in FeLV-positive cats. A special type of FeLV-associated enteritis (Reinacher, 1987) is also a new entity associated with persistent FeLV viremia.

Non-neoplastic diseases account for about three-quarters of the FeLV-as-

sociated diseases and only about 23% are neoplasms, mostly hematopoietic tumors. The spectrum of the non-neoplastic FeLV-associated diseases and conditions can only partially be explained by the immunosuppressive effect of FeLV. This immunosuppressive effect induces a very specific and selected susceptibility to secondary infections. Of these, mainly bacterial infections with streptococci, pasteurellas, and salmonellas are important whereas viral (with the exception of FIP), mycotic and parasitic (with the exception of flea infestation) infections were not associated closely with FeLV infection.

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