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Review paper

Clinical aspects of feline immunodeficiency and feline leukemia virus infection

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ABSTRACT

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are retroviruses with a global impact on the health of domestic cats. The two viruses differ in their potential to cause disease. FIV can cause an acquired immunodeficiency syndrome that increases the risk of developing opportunistic infections, neurological diseases, and tumors. In most naturally infected cats, however, FIV itself does not cause severe clinical signs, and FIV-infected cats may live many years without any health problems. FeLV is more pathogenic, and was long considered to be responsible for more clinical syndromes than any other agent in cats. FeLV can cause tumors (mainly lymphoma), bone marrow suppression syndromes (mainly anemia) and lead to secondary infectious diseases caused by suppressive effects of the virus on bone marrow and the immune system. Today, FeLV is less important as a deadly infectious agent as in the last 20 years prevalence has been decreasing in most countries.

Contents

Feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) are among the most common infectious diseases of cats. Belonging to the retroviral family, FIV is classified as a lentivirus, FeLV as a γ-retrovirus. Although FIV and FeLV are both retroviruses, they differ in their potential to cause disease. Vaccines are available for both viruses; however, identification and segregation of infected cats remain the cornerstone for preventing new infections (Levy et al., 2008). In the United States, prevalence of both infections is about 2% in healthy cats and up to about 30% in high-risk or sick cats (O'Connor et al., 1991; Levy et al., 2006). Risk factors for infection include male gender, adulthood, and outdoor access (Hoover and Mullins, 1991; Gleich and Hartmann, 2009). This article provides a comprehensive overview about clinical aspects of FIV and FeLV infection including pathophysiology and immunological background that is intended for both feline practitioners and investigators studying these diseases.

1. Feline immunodeficiency virus infection

FIV can cause an acquired immunodeficiency syndrome in cats, comparable to human immunodeficiency virus (HIV) infection in humans, with increased risk for opportunistic infections, neurologic diseases, and tumors. In a follow-up study in naturally FIV-infected cats, the rate of

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progression was variable, with death occurring in about 18% of infected cats within the first two years of observation (about five years after the estimated time of infection). An additional 18% developed increasingly severe disease, but more than 50% remained clinically asymptomatic during the two years (Barr, 2000). In a closed household of 26 cats, FIV infection did not adversely affect the cats' life expectancy (Addie et al., 2000).

Experimental FIV infection progresses through several stages, similar to HIV infection in people, including an acute phase, a clinically asymptomatic phase of variable duration, and a terminal phase sometimes named "feline acquired immunodeficiency syndrome" ("FAIDS") (English, 1995; Goto et al., 2000). In experimental infection, an initial stage (acute phase) is sometimes noticed with usually transient and mild clinical signs, including fever, lethargy, signs of enteritis, stomatitis, dermatitis, conjunctivitis, respiratory tract disease, and generalized lymph node enlargement (Obert and Hoover, 2000). The duration of the following asymptomatic phase varies but usually lasts many years. Factors that influence the length of the asymptomatic stage include the pathogenicity of the infecting isolate (also depending on the FIV subtype), exposure to secondary pathogens, and the age of the cat at the time of infection (Podell et al., 1997; Pedersen et al., 2001). In the last, symptomatic stage ("FAIDS phase") of infection, clinical signs are a reflection of opportunistic infections, neoplasia, myelosuppression, and neurologic disease.

In a survey study of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, the most common disease syndromes were stomatitis, neoplasia (especially lymphoma and cutaneous squamous cell carcinoma), ocular inflammation (uveitis and chorioretinitis), anemia and leukopenia, opportunistic infections, renal insufficiency, lower urinary tract disease, and endocrinopathies such as hyperthyroidism and diabetes mellitus (Levy, 2000a). Infections with many different "opportunistic" pathogens of viral, bacterial, protozoal, and fungal origin have been reported in FIV-infected cats. Few studies, however, have compared the prevalence of most of these infections in FIV-infected and non-infected cats, and thus, their relevance as true secondary invaders is unclear. Secondary infections are promoted by the immunosuppression caused be FIV through a progressive disruption of normal immune function. The most important immunologic abnormality demonstrated in experimental (Ackley et al., 1990; Barlough et al., 1991; Tompkins et al., 1991) as well as in natural (Novotney et al., 1990; Hoffmann-Fezer et al., 1992) infection is a decrease in the number and relative proportion of $CD4^+$ cells in the peripheral blood as well as in most primary lymphoid tissues (Bull et al., 2003). Loss of $CD4^+$ cells leads to inversion of the CD4/CD8 ratio. In addition, an increase in the proportion of $CD8^+$ cells also contributes to the inversion (Ackley et al., 1990; Hoffmann-Fezer et al., 1992; Willett et al., 1993), in particular a population referred to as "$CD8^+$ alpha-hi, beta-low cells" (Shimojima et al., 1998, 2003; Phadke et al., 2006), a subset of $CD8^+$ cells that may contribute to suppression of viremia in FIV-infected cats.

Causes of $CD4^+$ cell loss include decreased production secondary to bone marrow or thymic infection, lysis of infected cells induced by FIV itself (cytopathic effects), destruction of virus-infected cells by the immune system, or death by apoptosis (cell death that follows receipt of a membrane signal initiating a series of programmed intracellular events) (Bishop et al., 1993; Ohno et al., 1993, 1994; Johnson et al., 1996; Guiot et al., 1997a,b; Mizuno et al., 1997; Mortola et al., 1998a,b; Piedimonte et al., 1999; Mizuno et al., 2001, 2003b; Tompkins et al., 2002). The degree of apoptosis correlates inversely with $CD4^+$ numbers and the CD4/CD8 ratio (Holznagel et al., 1998). FIV *env* proteins are capable of inducing apoptosis in mononuclear cells by a mechanism that requires CXCR4 binding (Garg et al., 2004). Ultimately, loss of $CD4^+$ cells impairs immune responses because $CD4^+$ cells have critical roles in promoting and maintaining both humoral and cell-mediated immunity. A certain subset of $CD4^+$ cells, termed "Treg" (for T-regulatory cells), also seems to play an important role in FIV immunosuppression, and Treg cells with suppressive activity have been documented during early (Mexas et al., 2008) and chronic FIV infection (Petty et al., 2008). In FIV-infected cats, increased activity of Treg cells could thus play a role in suppressing immune responses to foreign antigens or pathogens. In addition, Treg cells are themselves targets for FIV infection (Joshi et al., 2005a,b; Mexas et al., 2008), and may serve as a FIV reservoir during the latent stage of infection capable of stimulating virus production (Joshi et al., 2004).

Several other immunologic abnormalities can be found in FIV-infected cats. Lymphocytes may loose the ability to proliferate in response to stimulation with mitogens or antigens, and priming of lymphocytes by immunogens may be impaired (Hara et al., 1990; Hosie and Jarrett, 1990; Taniguchi et al., 1990; Barlough et al., 1991; Taniguchi et al., 1991; Torten et al., 1991; Bishop et al., 1992a,b). Lymphocyte function may be reduced by altered expression of cell surface molecules, such as CD4, major histocompatibility complex II antigens, or cytokines and cytokine receptors (Willett et al., 1991; Ohno et al., 1992; Rideout et al., 1992; Choi et al., 2000; Mizuno et al., 2003a), or through over-expression of abnormal molecules, such as receptors (Nishimura et al., 2004), leading to disrupted cytokines production or receptor function. Impaired neutrophil adhesion and emigration in response to bacterial products have been described in FIV-infected cats (Hanlon et al., 1993; Kubes et al., 2003; Heit et al., 2006). Natural killer cell activity may be diminished (Zaccaro et al., 1995) or increased (Zhao et al., 1995) in acutely or asymptomatically infected cats, respectively. Changes in cytokine patterns include increased production of interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-4, IL-6, IL-10, and IL-12 (Lerner et al., 1998; Liang et al., 2000; Orandle et al., 2000; Ritchey et al., 2001), but also differences in cytokine ratios (e.g., IL-10/IL-12 ratio) (Dean et al., 1998; Lehman et al., 2009).

Another immunologic dysregulation observed in many FIV-infected cats is an excessive immune response leading to hypergammaglobulinemia (Ackley et al., 1990; Flynn et al., 1994; Gleich and Hartmann, 2009). Hypergammaglobulinemia reflects polyclonal B-cell stimulation and is a direct consequence of FIV infection, because healthy FIV-positive, specific pathogen-free (SPF) cats also develop

hypergammaglobulinemia (Flynn et al., 1994). In addition to increased IgG, increased circulating immune complexes have been detected in FIV-infected cats (Matsumoto et al., 1997), potentially leading to immune complex deposition disorders, such as glomerulonephritis and uveitis.

Chronic ulcero-proliferative stomatitis is the most common syndrome found in cats naturally infected with FIV (affecting up to 50%). It characteristically originates in the pharyngeal area and spreads rostrally, especially along the maxillary teeth. Lesions are often painful, and tooth loss is common. Severe stomatitis can lead to anorexia and emaciation. Histologically, the mucosa is invaded by plasma cells and lymphocytes, accompanied by variable degrees of neutrophilic and eosinophilic inflammation. The cause of this syndrome is uncertain, but the histologic findings suggest an immune response to chronic antigenic stimulation or immune dysregulation. Circulating lymphocytes of cats with stomatitis have greater than normal expression of inflammatory cytokines (Levy, 2000a), further implicating immune activation in the pathogenesis of this condition. This type of stomatitis is not always correlated with FIV infection (Quimby et al., 2008), and is usually not seen in experimentally FIV-infected specific pathogen-free cats, suggesting that exposure to other infectious agents also plays a role (Levy, 2000b). Concurrent feline calicivirus (FCV) infection is often identified in the oral cavity of these cats, and experimental and naturally occurring co-infection of FIV-infected cats with FCV results in more severe disease (Tenorio et al., 1991; Reubel et al., 1994).

Neurologic signs have been described in both natural and experimental in acute as well as chronic FIV infections (Dow et al., 1990, 1992; Podell et al., 1993; English et al., 1994; Phillips et al., 1994; Abramo et al., 1995). About 5% of clinically affected FIV-infected cats have a neurological disease as a predominant clinical feature. Neurologic disorders in FIV infection seem to be strain-dependent (Power et al., 1998). Both central and peripheral neurologic manifestations are seen, comparable to the changes in HIV-infected human beings. Dementia in human patients with AIDS is often characterized by a slight decline in cognitive ability or behavior, changes that may be too subtle to recognize in cats. Neurological abnormalities seen in naturally infected cats also tend to be more behavioral than motor. Twitching movements of the face and tongue, psychotic behavior, compulsive roaming, dementia, loss of bladder and rectal control, and disturbed sleep patterns have been obeserved. Other signs described include nystagmus, ataxia, seizures, and intention tremors (Prospero-Garcia et al., 1994; Gunn-Moore et al., 1996; Steigerwald et al., 1999). Abnormal forebrain electrical activity and abnormal visual and auditory-evoked potentials have also been documented in cats that appeared otherwise normal (Podell et al., 1997, 1999; Barr et al., 2000; Phipps et al., 2000). Although the majority of FIV-infected cats do not show clinically observable neurologic signs, a much higher proportion of infected cats exhibit microscopic CNS lesions. Brain lesions may occur in the absence of massive infection, and abnormal neurological function has been documented in FIV-infected cats with only mild to moderate histological evidence of inflammation (Barr, 2000). Pathologic findings include the presence of perivascular infiltrates of mononuclear cells, diffuse gliosis, glial nodules, and white matter pallor. These lesions are usually located in the caudate nucleus, midbrain, and rostral brain stem (Barr, 2000).

FIV enters the brain early following experimental infection, most likely *via* the blood–brain and blood–cerebrospinal fluid barriers. The exact mechanism of entry, and the factors that influence this entry, are not fully understood (Fletcher et al., 2010). Tumor necrosis factor (TNF)-alpha seems to play an important role in lymphocyte migration through the blood–brain barrier (Fletcher et al., 2010). Caused by the early brain infection, virus-induced CNS lesions sometimes develop within two months of experimental infection (Barr, 2000). Microglia and astrocytes are infected by FIV. The virus does not infect neurons. However, neuronal death has been associated with FIV infection; in particular, forebrain signs are often a result of direct neuronal injury from the virus. Neurologic expression of FIV infection is highly strain-dependent. The FIV envelope seems to be a principal determinant of neuropathogenesis because the envelope, which is a domain of extensive molecular diversity, directly influences neuropathogenesis through the activation of select proteases (Power et al., 2004). However, while envelope proteins of some FIV strains can promote neuronal swelling and death, envelope proteins of other strains have negligible toxicity (Bragg et al., 1999).

The exact mechanism of neuronal damage by FIV is unclear but may include neuronal apoptosis, effects on the neuron supportive functions of astroytes, toxic products released from infected microglia, or cytokines produced in response to viral infection. *In vitro* studies support the hypothesis that FIV infection may impair normal metabolism in CNS cells, particularly astrocytes (Barr, 2000). Documented abnormalities of astrocyte function include altered intercellular communication, abnormal glutathione reductase activity that could render cells more susceptible to oxidative injury, and alterations in mitochondrial membrane potential that disrupt energy-producing capacities of the cell (Sellon, 1998). Astrocytes are by far the most common cell type of the brain and are important in maintaining CNS neuronal mirovascular microenvironment. One of the most important functions of astrocyes is to regulate the level of extracellular glutamate, a major excitatory neurotransmitter that accumulates as a consequence of neuronal activity. Excessive extracellular glutamate often results in neuronal toxicity and death. FIV infection of feline astrocytes can significantly inhibit their glutamate-scavenging ability, potentially resulting in neuronal damage (Sellon, 1998, 2002; Sellon and Hartmann, 2006). Intracellular calcium levels seem to play a critical role, and changes in its levels may lead to neuronal dysfunction (Meeker, 2007). It has been shown that choroid plexus macrophages proliferate and release toxic factors in response to FIV (Bragg et al., 2002), and that these factors destabilize neuronal calcium homeostasis (Bragg et al., 2002). Thus, choroid plexus macrophages may contribute to an inflammatory cascade in the brain that progresses independently of systemic and CSF viral load.

CSF changes described in FIV-infected cats with neurologic disease include cellular pleocytosis and increases in concentrations of IgG (Dow et al., 1990). Viral RNA may be

detected in the CSF of some cats and suggests parenchymal infection (Ryan et al., 2003).

FIV-infected cats are about five times more likely to develop lymphoma or leukemia than non-infected cats and have a higher incidence of certain types of tumors (Poli et al., 1994; Callanan et al., 1996). Lymphomas (mostly B-cell lymphomas) (Poli et al., 1994; Terry et al., 1995; Callanan et al., 1996; Gabor et al., 2001), leukemias, and a variety of other tumors have been described in association with FIV infection (Fleming et al., 1991; Hutson et al., 1991; Buracco et al., 1992; Callanan et al., 1992; Poli et al., 1994; Court et al., 1997; Barr et al., 2000), including squamous cell carcinoma, fibrosarcoma, and mast cell tumor. FIV provirus, however, is only occasionally detected in tumor cells (Beatty et al., 1998a,b, 2002; Wang et al., 2001) suggesting a more indirect role in lymphoma formation, such as decreased cell-mediated immune surveillance or chronic B-cell hyperplasia (Endo et al., 1997; Beatty et al., 1998b). However, clonally integrated FIV DNA was found in lymphoma cells from one cat that had been experimentally infected six years earlier (Diehl and Hoover, 1992; Beatty et al., 1998a, 2002) indicating the possibility of an occasional direct oncogenic role of FIV in some animals. The prevalence of FIV infection in one cohort of cats with lymphoma was 50% (Gabor et al., 2001), much higher than the FIV prevalence in the population of cats without lymphomas, which is also supportive of a cause and effect relationship. Beside causing a direct effect, FIV may alternatively increase cancer incidence by decreasing tumor immunosurveillance mechanisms, may promote tumor development through the immunostimulatory effects of replicating in lymphocytes, or may impair immunological control of FeLV infection and accelerate the proliferation of transformed lymphoid cells.

2. Feline leukemia virus infection

FeLV is more pathogenic than FIV. Historically, FeLV was considered to account for most disease-related deaths and to be responsible for more clinical syndromes than any other single agent in cats. It was proposed that approximately one-third of all tumor-related deaths in cats were caused by FeLV, and an even greater number of cats died of FeLV-related anemia and secondary infectious diseases caused by suppressive effects of the virus on bone marrow and the immune system. Today, these statements have to be revised, as in recent years prevalence and consequently importance of FeLV as a pathogen in cats have been decreasing. Still, if present in closed households with endemic feline coronavirus (FCoV), FeLV, FIV, or all of these infections, FeLV infection has the greatest impact on mortality (Addie et al., 2000). The death rate of progressively FeLV-infected cats in multi-cat households is approximately 50% in two years and 80% in three years (Cotter, 1998; Levy, 2000c), but much lower for cats kept strictly indoors in single-cat households. A large study in the United States compared the survival of more than 1000 FeLV-infected cats to more than 8000 age- and sex-matched uninfected control cats and found that in FeLV-infected cats median survival was 2.4 years compared to 6.0 years for control cats (Levy et al., 2006).

Clinical signs associated with FeLV infection are variable. Although the virus was named after the contagious tumor that first garnered its attention, most infected cats are presented to the veterinarian not for tumors but for anemia or immunosuppression. Of 8642 FeLV-infected cats examined at North American Veterinary Teaching Hospitals, various co-infections (including FIV infection, FIP, upper respiratory infection, hemotropic mycoplasmosis, and stomatitis) were the most frequent findings (15%), followed by anemia (11%), lymphoma (6%), leukopenia or thrombocytopenia (5%), and leukemia or myeloproliferative disease (4%) (Cotter, 1991). The exact mechanisms for the different clinical responses in progressively FeLV-infected cats are poorly understood. It is clear that the clinical course is determined by a combination of viral and host factors. Some of these differences can be traced to properties of the virus itself, such as the subgroup that determines differences in the clinical picture (e.g., FeLV-B is primarily associated with tumors, FeLV-C is primarily associated with non-regenerative anemia).

Flynn et al. (2002) examined dominant host immune effector mechanisms responsible for the outcome of infection by using longitudinal changes in FeLV-specific cytotoxic T-lymphocytes (CTL). High levels of circulating FeLV-specific effector CTLs appear before virus-neutralizing antibodies in cats that have recovered from exposure to FeLV. In contrast, progressive infection with persistent viremia has been associated with a silencing of virus-specific humoral and cell-mediated immunity host effector mechanisms (Flynn et al., 2002). It is likely that the most important host factor that determines the clinical outcome of cats infected with FeLV is the age of the cat at the time of infection (Hoover et al., 1976). Neonatal kittens develop marked thymic atrophy after infection ("fading kitten syndrome"), resulting in severe immunosuppression, wasting, and early death. As cats mature, they acquire a progressive resistance. When older cats become infected, they tend to have abortive or regressive infections or, if developing progressive infection, have at least milder signs and a more protracted period of apparent good health (Levy, 2000c).

Clinical signs associated with FeLV infection can be classified as tumors, immunosuppression, hematologic disorders, immune-mediated diseases, and other syndromes (including neuropathy, reproductive disorders, fading kitten syndrome). Immunosuppression is caused by various mechanisms in FeLV-infected cats. It has been occasionally associated with un-integrated viral DNA from replication-defective viral variants (Overbaugh et al., 1988). These pathogenic immunosuppressive variants, such as FeLV-T, require a membrane-spanning receptor molecule (Pit1) and a second co-receptor protein (FeLIX) to infect T lymphocytes (Lauring et al., 2002). The latter protein is an endogenously expressed protein, which is similar to the FeLV receptor-binding protein of FeLV-B (Barnett et al., 2003).

Affected cats may develop thymic atrophy and depletion of lymph node paracortical zones following infection. Lymphopenia and neutropenia are common. In addition, neutrophils of progressively infected cats have decreased chemotactic and phagocytic function compared with those

of normal cats. In some cats, lymphopenia may be characterized by preferential loss of $CD4^+$ helper T cells, resulting in an inverted CD4/CD8 ratio (like typically seen in FIV infection) (Quackenbush et al., 1990; Hoffmann-Fezer et al., 1996), but more commonly, substantial losses of helper cells and cytotoxic suppressor cells ($CD8^+$ cells) occur (Hoffmann-Fezer et al., 1996). Many immune function tests of naturally FeLV-infected cats are abnormal, including decreased response to T-cell mitogens, prolonged allograft reaction, reduced immunoglobulin production, depressed neutrophil function, and complement depletion. IL-2 and IL-4 are decreased in some cats (Linenberger and Deng, 1999; Levy, 2000c), but FeLV does not appear to suppress IL-1 production from infected macrophages. IFN-γ may be deficient or increased. Increased TNF-α has been observed in serum of infected cats and in infected cells in culture. Each cytokine plays a vital role in the generation of a normal immune response, and the excess production of certain cytokines such as TNF-α can also cause illness. T-cells of FeLV-infected cats produce significantly lower levels of B-cell stimulatory factors than do those of normal cats (this defect becomes progressively more severe over time) (Diehl and Hoover, 1992), but when B-cells of FeLV-infected cats are stimulated *in vitro* by uninfected T-cells, their function remains normal. In vaccination studies, FeLV-infected cats have not been able to mount an adequate immune response to vaccines, such as rabies. Therefore, protection in a FeLV-infected cat after vaccination is not complete and comparable to that in a healthy cat, and more frequent vaccinations (e.g., every six months) have to be considered (Lutz et al., 2009).

In addition to immunosuppression, FeLV-infected cats can develop immune-mediated diseases caused by an overactive or dysregulated immune response to the virus. Although humoral immunity to specific stimulation decreases, nonspecific increases of IgG and IgM have been noted. The loss of T-cell activity and the formation of antigen antibody complexes promote the immune dysregulation (Pedersen, 1988). Immune-mediated diseases described in FeLV-infected cats include AIHA (Kohn et al., 2006), glomerulonephritis (Anderson and Jarrett, 1971), uveitis with immune complex deposition in iris and ciliary body (Brightman et al., 1991), and polyarthritis (Pedersen, 1991). Chronic progressive polyarthritis can be triggered by FeLV; in about 20% of cats with polyarthritis, FeLV seems to be an associated agent (Pedersen, 1991). Cats with glomerulonephritis have more circulating FeLV antigen that do other FeLV-infected cats. However, in a recent study FeLV-infected cats in general did not show significantly more commonly hypergammaglobulinemia in plasma electrophoretogram in contrast to FIV-infected cats (Miro et al., 2007), and hyperproteinemia is not a common problem in FeLV-infected cats (in contrast to FIV infection) (Gleich and Hartmann, 2009). Antigens that can lead to antigen antibody complex formation include not only whole virus particles but also free gp70, p27, or p15E proteins (Day et al., 1980; Tuomari et al., 1984).

Hematopoietic disorders, particularly cytopenias caused by bone marrow suppression, are a common finding in FeLV-infected cats. Hematologic disorders described in association with FeLV include anemia (non-regenerative or regenerative), persistent, transient, or cyclic neutropenia, platelet abnormalities (thrombocytopenia and platelet function abnormalities), aplastic anemia (pancytopenia), and panleukopenia-like syndrome. For the majority of pathogenic mechanisms in which FeLV causes bone marrow suppression, active virus replication is required. However, it has been demonstrated that in some FeLV antigen-negative cats, regressive FeLV infection without viremia may be responsible for bone marrow suppression. In a recent study including 37 cats with myelosuppression that had tested FeLV antigen-negative in peripheral blood, 2/37 cats (5%) were found regressively infected with FeLV by bone marrow PCR (both had non-regenerative anemia) (Stützer et al., 2010). In these cats, FeLV provirus may interrupt or inactivate cellular genes in the infected cells, or regulatory features of viral DNA may alter expression of neighboring genes. Additionally, cell function of provirus-containing myelomonocytic progenitor and stromal fibroblasts that provide bone marrow microenvironment may be altered. Alternatively, FeLV provirus may cause bone marrow disorders by inducing the expression of antigens on the cell surface, resulting in an immune-mediated destruction of the cell.

Anemia is a major non-neoplastic complication that occurs in a majority of symptomatic FeLV-infected cats (Gleich and Hartmann, 2009). Anemia in FeLV-infected cats may have various causes. Approximately 10% of FeLV-associated anemias are regenerative (Shelton and Linenberger, 1995), most FeLV-associated anemias, however, are non-regenerative and caused by the bone marrow-suppressive effect of the virus resulting from primary infection of hematopoietic stem cells and infection of stroma cells that constitute the supporting environment for hematopoietic cells. *In vitro* exposure of normal feline bone marrow to some strains of FeLV causes suppression of erythrogenesis (Cotter, 1998). In addition to the direct effect of the virus on erythropoiesis, other factors can cause non-regenerative anemia in FeLV-infected cats (e.g., anemia of chronic disease promoted by high concentration of cytokines). FeLV infection may cause decreased platelet counts. It also may be responsible for platelet function deficits, and the lifespan of platelets is shortened in some FeLV-infected cats. Thrombocytopenia (resulting in bleeding disorders) may occur secondary to decreased platelet production from FeLV-induced bone marrow suppression or leukemic infiltration. Platelets harbor FeLV proteins as a result of infection, and megakaryocytes are frequent targets of progressive FeLV infection. Immune-mediated thrombocytopenia often accompanies IMHA in cats with underlying FeLV infection. FeLV infection also may cause decreased neutrophil or lymphocyte counts. Neutropenia is common in FeLV-infected cats (Brown and Rogers, 2001) and generally occurs alone or in conjunction with other cytopenias. In some cases, myeloid hypoplasia of all granulocytic stages is observed, suggesting direct cytopathic infection on neutrophil precursors by FeLV. In some neutropenic FeLV-infected cats, an arrest in bone marrow maturation may occur at the myelocyte and metamyelocyte stages. Immune-mediated mechanisms may alternatively be responsible in cases in which

neutrophil counts recover with glucocorticoid treatment ("glucocorticoid-responsive neutropenia").

Feline panleukopenia-like syndrome (FPLS), also known as FeLV-associated enteritis (FAE) or myeloblastopenia, consists of severe leukopenia (<3000 cells/μl) with enteritis and destruction of intestinal crypt epithelium that mimics feline panleukopenia caused by feline panleukopenia virus (FPV) infection. However, FPV antigen has been demonstrated by IFA in intestinal sections of cats that died from this syndrome after being experimentally infected with FeLV (Lutz et al., 1995). FPV was also demonstrated by electron microscopy despite negative FPV antigen tests. It appears that this syndrome may actually not be caused by FeLV itself, as previously thought, but by co-infection with FPV. The syndromes also has been referred to as FAE in cats with progressive FeLV infection because the clinical signs observed are usually gastronintestinal, including hemorrhagic diarrhea, vomiting, oral ulceration or gingivitis, anorexia, and weight loss (Kipar et al., 2000, 2001). It is still unclear whether all these syndromes have the same origin and are simply caused by co-infection with FPV (and even modified life FPV vaccines have been discussed) or if they are caused by FeLV itself (Lutz et al., 1995).

Hematopoietic neoplasia ("myeloprolifertaive disorders"), including leukemia, may also cause bone marrow suppression syndromes by replacing bone marrow cells. Myelodysplastic syndrome (MDS), characterized by peripheral blood cytopenias and dysplastic changes in the bone marrow, is a pre-stage of acute myeloic leukemia. It was found that changes of the LTR of FeLV (presence of three tandem direct 47-bp repeats in the upstream region of the enhancer (URE)) are strongly associated with the induction of MDS (Hisasue et al., 2009). Myelofibrosis, another bone marrow suppression syndrome characterized by abnormal proliferation of fibroblasts resulting from chronic stimulation of the bone marrow, such as chronic bone marrow activity from hyperplastic or neoplastic regeneration, may also be caused by FeLV. In severe cases, the entire endosteum within the medullary cavity can be obliterated.

FeLV can cause different tumors in cats, most commonly lymphoma and leukemia, less commonly other hematopoietic tumors. The most important mechanism by which FeLV causes malignancy is by insertion of the FeLV genome into the cellular genome near a cellular oncogene (most commonly *myc*), resulting in activation and over-expression of that gene. These effects lead to uncontrolled proliferation of that cell (clone). A malignancy results in the absence of an appropriate immune response. FeLV-A may also incorporate the oncogene to form a recombinant virus (e.g., FeLV-B, FeSV) containing cellular oncogene sequences that are then rearranged and activated. When they enter a new cell, these recombinant viruses are oncogenic. In a study of 119 cats with lymphomas, transduction or insertion of the *myc* locus had occurred in 38 cats (32%) (Tsatsanis et al., 1994). Thus, FeLV-induced neoplasms are caused, at least in part, by somatically acquired insertional mutagenesis in which the integrated provirus may activate a proto-oncogene or disrupt a tumor suppressor gene. A recent study suggested that the U3-LTR region of FeLV transactivates cancer-related signaling pathways through production of a non-coding 104 base RNA transcript that activates NF kappaB (Forman et al., 2009). Common integration sites for FeLV associated with lymphoma development have been identified in six loci: *c-myc*, *flvi-1*, *flvi-2* (contains *bmi-1*), *fit-1*, *pim-1*, and *flit-1*. Oncogenic association of the loci has been suggested because *c-myc* is known as a proto-oncogene, *bmi-1* and *pim-1* have been recognized as *myc*-collaborators, *fit-1* appears to be closely linked to *myb*, and *flit-1* insertion was shown to be associated with over-expression of cellular genes, e.g., activin-A receptor type II-like 1 (*ACVRL1*) (Fujino et al., 2008). *Flit-1* especially seems to play an important role in the development of thymic lymphomas and appears to represent a novel FeLV proviral common integration domain that may influence lymphomagenesis through insertional mutagenesis. Among 35 FeLV-related tumors, five of 25 thymic lymphomas demonstrated proviral insertion within *flit-1* locus, whereas none of four alimentary, five multicentric lymphomas, and one T-lymphoid leukemia examined had rearrangement in this region. Expression of *ACVRL1* mRNA was detected the two thymic lymphomas with *flit-1* rearrangement, whereas normal thymuses and seven lymphoid tumors without *flit-1* rearrangement had no detectable *ACVRL1* mRNA expression (Fujino et al., 2009).

The association between FeLV and lymphomas has been clearly established in several ways. First, these malignancies can be induced in kittens by experimental FeLV infection (Rickard et al., 1969; Hardy et al., 1973; Jarrett et al., 1973). Second, cats naturally infected with FeLV have a higher risk of developing lymphoma than uninfected cats (Hardy et al., 1973; Essex et al., 1975). Third, most cats with lymphoma were – at least in earlier times when prevalence of FeLV was still higher – FeLV-positive in tests that detected infectious virus or FeLV antigens. Previously, up to 80% of feline lymphomas and leukemias were reported to be FeLV related (Cotter et al., 1975; Francis et al., 1977, 1979; Hardy et al., 1980; Reinacher, 1987; Shelton et al., 1990; Harrus et al., 2002). However, since 1980, a dramatic reduction in the prevalence of viremia has been noted in cats with lymphoma (Mauldin et al., 1995; Moore et al., 1996; Hartmann et al., 1998). The decrease in prevalence of FeLV infection in cats with lymphoma or leukemia also indicates a shift in tumor causation in recent years. Whereas 59% of all cats with lymphoma or leukemia were FeLV antigen-positive in one German study from 1980 to 1995, only 20% of the cats were FeLV antigen-positive in the years 1996 to 1999 in the same university veterinary clinic (Hartmann et al., 1998). A recent study in this area confirmed the low prevalence of FeLV antigenemia in cats with lymphoma; in the study, 16 of 77 cats (21%) were FeLV antigen-positive (Stützer et al., 2011). In a study in the Netherlands, only four of 71 cats with lymphoma were FeLV-positive, although 22 of these cats had mediastinal lymphoma, which was previously highly associated with FeLV infection (Teske et al., 2002). Today, a higher lymphoma incidence in older FeLV antigen-negative cats is observed. The major reason for the decreasing association of FeLV with lymphoma is the decreasing prevalence of FeLV infection in the overall cat population as a result of FeLV vaccination as well as testing and elimination programs. However, prevalence of

lymphoma caused by FeLV may be higher than indicated by conventional antigen testing of blood. Cats from FeLV cluster households had a 40-fold higher rate of development of FeLV-negative lymphoma than did those from the general population. FeLV-negative lymphomas have also occurred in laboratory cats known to have been infected previously with FeLV (Rohn et al., 1994). FeLV proviral DNA was detected in lymphomas of older cats that tested negative for FeLV antigen, also suggesting that the virus may be associated with a larger proportion of lymphomas than previously thought. PCR detected proviral DNA in formalin-fixed, paraffin-embedded tumor tissue in seven of 11 FeLV-negative cats with lymphoma (Jackson et al., 1993). However, other groups found evidence of provirus in only one of 22 (Sheets et al., 1993) or in none of 61 FeLV antigen-negative lymphomas (Hartmann et al., 1998). The FeLV status of cats with lymphomas still varies, depending on the type and locations of tumors. Lymphomas in FeLV antigen-positive cats are mainly of a T-cell origin; those in FeLV antigen-negative cats are mainly of a B-cell origin (Hardy et al., 1977; Francis et al., 1979; Hardy, 1981; Neil et al., 1984). This was confirmed in a recent study in which 8/28 (64.3%) FeLV antigen-negative cats with lymphoma had T-cell lymphoma, while none of the FeLV antigen-positive cats (0/8) had B-cell lymphoma (Stützer et al., 2011). A potential reason may be that FeLV transforms mature T cells and immature or prothymocytes, null cells, and possibly monocytes. Transformation of mature B cells does not seem to occur, because feline lymphoma cell lines and primary tumors lack surface immunoglobulin expression (Rojko et al., 1989). The rare feline large granular lymphocyte (LGL) lymphoma, a morphologically distinct variant of feline lymphoma with grave prognosis, does not seem to be commonly associated with FeLV. In a study of 45 cats with LGL lymphoma, none of the cats was FeLV antigen-positive (Krick et al., 2008). Similarly, low grade lymphomas are usually not associated with FeLV; in a study of 41 low grade lymphocytic lymphomas, none of the cats was FeLV antigen-positive (Kiselow et al., 2008).

Fibrosarcomas that are associated with FeLV are caused by FeSV, a recombinant virus that develops *de novo* in FeLV-A-infected cats by recombination of the FeLV-A genome with cellular oncogenes (Besmer et al., 1986). Through a process of genetic recombination, FeSV acquires one of several oncogenes, such as *fes, fms*, or *fgr* (Besmer et al., 1983). As a result, FeSV is an acutely transforming (tumor-causing) virus, leading to a polyclonal malignancy with multifocal tumors arising simultaneously after a short incubation period (McDonald et al., 1976; Pedersen et al., 1984). With the decrease in FeLV prevalence, FeSV also has become less common. FeSV-induced fibrosarcomas are multicentric and usually occur in young cats. Strains of FeSV identified from naturally occurring tumors are defective and unable to replicate without the presence of FeLV-A as a helper virus that supplies proteins (such as those coded by the *env* gene) to FeSV (Rojko et al., 1994). Fibrosarcomas caused by FeSV tend to grow rapidly, often with multiple cutaneous or subcutaneous nodules that are locally invasive and metastasize to the lung and other sites (Pedersen et al., 1984). Solitary fibrosarcomas in older cats are not caused by FeSV. These tumors are slower growing, locally invasive, slower metastasizing, and occasionally curable by excision combined with radiation and/or gene therapy. These tumors are usually injection site-associated sarcomas (ISAS) caused by the granulomatous inflammatory reaction at the injection site, commonly occurring after inoculation of adjuvant-containing vaccines. It has been demonstrated that neither FeSV nor FeLV play any role in ISAS (Ellis et al., 1996).

A number of other tumors have been found in FeLV-infected cats; some of them may have an association with FeLV, others have just been observed by chance simultaneously in an infected cat. Iris melanomas, for example, are not associated with FeLV infections. An association has been hypothesized because of one study in which three of 18 eyes had positive test results for FeLV-FeSV proviral DNA (Stiles et al., 1999). However in a more recent study, immunohistochemical staining and PCR did not reveal FeLV or FeSV in the ocular tissues of any cats with this disorder (Cullen et al., 2002). Multiple osteochondromas (cartilaginous exostoses on flat bones of unknown pathogenesis) have been described in FeLV-infected cats. Although histologically benign, they may cause significant morbidity if they occur in an area such as a vertebra and put pressure on the spinal cord or nerve roots (Pool and Carrig, 1972; Lott-Stolz, 1988). In spontaneous feline olfactory neuroblastomas (aggressive, histologically inhomogenous tumors of the tasting and smelling epithelium of nose and pharynx with high metastasis rates), budding FeLV particles were found in the tumors and lymph node metastases, and FeLV DNA was found in tumor tissue (Schrenzel et al., 1990). The exact role of FeLV in the genesis of these tumors is uncertain. Cutaneous horns are a benign hyperplasia of keratinocytes that have been described in FeLV-infected cats (Pedersen, 1991), but again the role of FeLV is unclear.

Other syndromes directly caused by FeLV infection include FeLV-associated neuropathy, reproductive disorders, and fading kitten syndrome. Although most neurologic signs seen in FeLV-infected cats are caused by lymphoma and lymphocytic infiltrations in brain or spinal cord leading to compression, in some cases no tumor is detectable with diagnostic imaging methods or in necropsy, and FeLV-induced neurotoxicity is suspected. Anisocoria, mydriasis, central blindness, or Horner's syndrome have been described in FeLV-infected cats without morphologic changes. In some regions (such as the southeastern United States), urinary incontinence caused by neuropathies in FeLV-infected cats has been described (Carmichael et al., 2002). Direct neurotoxic effects of FeLV have been discussed as pathogenetic mechanisms. FeLV envelope glycoproteins may be able to produce increased intracellular free calcium leading to neuronal death (this has also been described in HIV-infected humans). A polypeptide of the FeLV envelope was found to cause dose-dependent neurotoxicity associated with alterations in intracellular calcium ion concentration, neuronal survival, and neurite outgrowth. The polypeptide from an FeLV-C strain was significantly more neurotoxic than the same peptide derived from an FeLV-A strain (Fails et al., 1997; Mitchell et al., 1997). Clinical signs in 16 cats with progressive FeLV infection and neurologic signs consisted of abnormal vocalization, hyperesthesia, and paresis pro-

gressing to paralysis. Some cats developed anisocoria or urinary incontinence during the course of their illness. Affected cats developed gradually progressive neurologic dysfunction. Microscopically, white-matter degeneration with dilation of myelin sheaths and swollen axons was identified in the spinal cord and brain stem of affected animals (Carmichael et al., 2002). Immunohistochemical staining of affected tissues revealed consistent expression of FeLV p27 antigens in neurons, endothelial cells, and glial cells, and proviral DNA was amplified from multiple sections of spinal cord (Carmichael et al., 2002). These findings suggest that in some FeLV-infected cats, the virus may directly affect CNS cells cytopathically.

FeLV-infected queens can transmit the virus transplacentally. Reproductive failure in form of fetal resorption, abortion, and neonatal death is common if *in utero* FeLV infection occurs. The apparent infertility might actually be caused by early resorption of fetuses. Abortions usually occur late in gestation, with expulsion of normal appearing fetuses. Bacterial endometritis may accompany these abortions, particularly in cats with neutropenia (Cotter, 1998).

Kittens born to infected queens may become exposed to FeLV transplacentally, but heavy exposure also occurs at birth and throughout the nursing period. Some kittens become immune, but most become progressively infected and die at an early age of the so-called fading kitten syndrome, characterized by failure to nurse, dehydration, hypothermia, thymic atrophy, and death within the first two weeks of life (Levy, 2000c).

3. Discussion

Most knowledge about clinical aspects of FIV and FeLV infection as well as on the pathophysiology and immunological background of both infections derive from experimental studies. However, the relevance of these experimental data to the naturally occurring disease is unclear, and it remains an unanswered question on how or whether the experimental data can be applied to the clinical setting in the field. It is the impression of many clinicians that in most naturally infected cats, FIV does not cause a severe clinical syndrome. Most clinical signs in FIV-infected cats reflect secondary diseases such as infections and neoplasia to which FIV-infected cats are considered more susceptible. With proper care, FIV-infected cats can live many years and, in fact, may die at an old age from causes unrelated to their FIV infection. Although FeLV causes more severe clinical syndromes, and despite the fact that progressive FeLV infection is associated with a decrease in life expectancy, many owners still elect to provide therapy for their FeLV-infected cats, and with proper treatment, FeLV-infected cats in single-cat households may also live for many years with good quality of life. As in FIV infection, diseases secondary to immunosuppression account for a large portion of the syndromes seen in FeLV-infected cats, and it is important to realize that many of these secondary diseases are treatable. Many reports have been made of FeLV-infected cats having concurrent bacterial, viral, protozoal, and fungal infections, but few studies exist proving that these cats have a higher rate of infection than do FeLV-negative cats. Thus, although FeLV certainly can suppress immune function, it should not be assumed that all concurrent infections are a direct consequence of FeLV infection. While long-term studies describing clinical outcomes of naturally occurring FIV and FeLV infection are lacking, modalities for treatment of secondary infections or other co-incident diseases are in many cases available, and by treating these symptomatically, the life expectancy and quality of life of FIV- and FeLV-infected animals can be significantly enhanced. Studies that compare FIV- and FeLV-related secondary complications (e.g., infections, tumors) with the prevalence of these diseases in the absence of FIV and FeLV infection need to be performed in naturally occurring studies to definitively demonstrate these associations.

Conflict of interest

There was no conflict of interest associated with this article.

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