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Feline Immunodeficiency

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1. Introduction

Classic infectious causes of immunodeficiency in felines are the immunodeficiency by retroviruses, including feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). Immunodeficiency caused by these infectious agents may result from disruption of normal host barriers or deregulation of cellular immunity.

The feline immunodeficiency virus and the feline leukemia virus are detected worldwide and are among the most common infectious diseases of domestic cats, others small felids and wild cats, and causes immunodeficiency, with increased risk for opportunistic infections, neurologic diseases, and tumors.

Feline immunodeficiency virus and feline leukemia virus are retrovirus, but they differ in their potential to cause disease. FIV is classified as a *Lentivirus* and, FeLV as a *Gamaretrovirus*. The high incidence of FIV and FeLV is associated with density of cat population.

FIV causes immune dysfunctions in cats similar to those observed in people infected with human immunodeficiency virus (HIV). Diseases associated with FeLV and FIV may affect some organ, and may cause among other disorders, lymphoma, blood dyscrasias, alterations in the function of central nervous system, and secondary and opportunistic infections, with a significant number of opportunistic pathogens of viral, bacterial, protozoal, and fungal origin. Therefore, infected animals may play a role in transmission of various pathogens to human beings.

Risk groups for infection with FIV and FeLV are different: FIV is mainly associated with males, free access to streets and bites inflicted during fights for territory, therefore, the risk of FIV transmission is low in socially well-adapted cats, while FeLV infection is associated with social contacts and thus the FeLV infection is found almost equally between males and females, at a rate slightly elevate in male cats.

The diagnosis of FIV and FeLV can not be done based solely on clinical signs, but should be based on the demonstration of anti-FIV and FeLV antigen in the serum of infected animals.

FeLV and FIV do not survive for long outside the host and are easily inactivated by disinfectants, heating and drying. As prophylaxis against infection of FIV and FeLV is recommended castration to reduce aggression and lessen the bite. The rapid and accurate diagnosis of any secondary diseases is essential. In shelters, infected cats should be housed individually to prevent infection. All animals should be tested before being placed in shelters and breeding. Vaccines are available for both viruses; however, identification and segregation of infected cats remains the cornerstone for preventing new infections.

Studies and research about these viruses are continuously necessary to define prophylactic, management, and therapeutic measures for stray, feral and owned cats.

2. Feline immunodeficiency virus

The first isolation of feline immunodeficiency virus (FIV) has been described by Pedersen, 1987 in the city of Petaluma, USA. FIV is an important lentivirus that causes immune disorders in both domestic and nondomestic cats.

Like other retroviruses the FIV containing accessory genes in addition to *gag*, *pol* and *env*. The FIV *gag*, *pol* and *env* genes encode the capsid protein p24; protease, integrase, and reverse transcriptase proteins; the viral glycoprotein (gp120) and the transmembrane protein (gp41), respectively. Both *gag* and *pol* are relatively conserved between strains (Olmsted et al., 1989; Kenyon & Lever, 2011; McDonnel et al., 2012).

Species-specific strains of FIV circulate in many feline populations. Five genetically distinct subtypes or clades of FIV have been described: A, B, C, D and E, with considerable sequence diversity in the *env* gene. Studies have shown that is possible to use the *env* nucleotide sequence and the p17-p24 region of the *gag* gene for subtypes identification but, once *gag* gene has a retention rate higher than the *env* gene, it is considered a good candidate for phylogenetic studies (Sodora et al., 1994; Kurosawa et al., 1999; Hosie et al., 2009; Kenyon & Lever, 2011).

2.1. Epidemiology and transmission

The seroprevalence of FIV is highly variable between geographic locations. Epidemiological studies show that FIV transmission is influenced by behavior: cats with free access to the streets, sick cats, and males are more susceptible to infection with FIV (Courchamp & Pontier, 1994; Sellon and Hatmann, 2006).

Feline immunodeficiency virus can be transmitted primarily by inoculation of virus present in saliva or blood, presumably by bite and fight wounds. Male cats with free access to streets are more susceptible to infection because males are territorialist, other ways such as via mucosal exposure, blood transfer, during mating, and vertically during prenatal and postnatal exposure, can also be responsible for transmission. In natural infections, the

efficacy of colostral immunity is not known (Sellon & Hartmann, 2006; Medeiros et al., 2012).

2.2. Pathogenesis, immunity and clinical symptoms

FIV has a tropism for T cells, macrophages, dendritic cells and central nervous system cells. The major targets for FIV infection are activated CD4⁺ T lymphocytes (Fig. 1). These cells typically function as T helper cells, which have a central role in immune functions, facilitating the development of humoral and cell-mediated immunity (Fig. 1) (Sellon and Hartmann, 2006; Hosie et al., 2009; Simões et al., 2012). FIV does not use CD4 as a primary *binding* receptor, its gp120 glycoprotein binds to the CD134 (OX40) a member of the tumor necrosis factor receptor (TNFR)/nerve growth factor receptor family of molecules as the binding receptor in conjunction with the chemokine receptor CXCR4 as a cofactor for infection (Yuan et al., 2003; de Parseval et al., 2005; Willett et al., 2006b; Elder et al., 2010). The CD134 co-stimulatory pathway has been shown to be critical for T, B and antigen-presenting cell (APC) cell activation. Studies have shown that antigen stimulation of infected B-cells is increased compared with non-infected cells. FIV-infection in cats also results in a sustained polyclonal activation of B-cells with the production of antibodies to a variety of non-viral antigens (Yuan et al., 2003; Willett et al., 2006b).

Figure 1. Diagram illustrating the stages of the pathogenesis of FIV. Modified from Sellon and Hartmann, 2006.

As for HIV, it has been classified some stages for FIV infection (Table 1 and Fig. 2 and 3): clinical symptoms during initial stages (acute phase) of infection include fever, leucopenia, gingivitis, lethargy, signs of enteritis, stomatitis, dermatitis, conjunctivitis, respiratory tract disease, neutropenia, and generalized lymphadenopathy (Sellon e Hartmann, 2006; Gunn-Moore & Reed, 2011; Hartmann, 1998; Hartamann, 2011; O'Brien et al., 2012). The progression of disease occurs in a manner similar to the HIV-1 infection in humans. In the first few days after infection, FIV replicates in dendritic cells, macrophages and CD4+ T lymphocytes, within 2 weeks appears in the plasma. FIV-specific CD8+ cytotoxic T cells are detected in the blood within one week of infection. The duration of the following asymptomatic phase varies but usually lasts many years, viral replication is controlled by the immune response, but there is a progressive decline in CD4+ T lymphocyte numbers, resulting in a decreased CD4+/CD8+ T lymphocyte ratio (Fig. 1) (Hartmann, 1998; Sellon e Hartmann, 2006; Gunn-Moore & Reed, 2011; Hartamann, 2011). The most infected cats exhibit an increase in CD8+ T cells along with a strong humoral antibody response which allows them to control this initial phase of the infection (Elder et al., 2010). After 2-4 weeks after infection, antibodies are detectable in plasma for FIV. Antibodies recognizing *env* related proteins appear earlier than those against the *gag* protein p24. Factors that influence the length of the asymptomatic stage include the pathogenicity of the infecting strain (also depending on the FIV subtype), exposure to secondary pathogens, and the age of the cat at the time of infection. In the last, symptomatic stage (FAIDS phase) of infection, clinical signs are a reflection of opportunistic infections, skin infections such as demodicosis and pediculosis, neoplasia such as B cell lymphosarcoma and squamous cell carcinoma, myelosuppression, and neurologic disease, similar to those observed in people infected with human immunodeficiency virus (HIV) (Hartmann, 1998; Sellon e Hartmann, 2006; Elder et al., 2010; Gunn-Moore & Reed, 2011; Hartamann, 2011; Korman et al., 2012; Sobrinho et al., 2012). The chronic gingivostomatitis is the most common clinical sign in infected cats and significantly degrade the quality of life of animals

Phases	Clinical sings	Duration
Acute Unspecific signs	Neutropenia, Fever, lethargy, peripheral, lymphadenopathy, weight loss	Weeks-months
Asymptomatic	No clinical signs, but there is a progressive decline in CD4+ T lymphocyte numbers	Years
Unspecific clinical signs	Apathy, weight loss, lymphadenopathy, fever, anorexia, depression, chronic gingivostomatitis (difficulty eating), chronic rhinitis, lymph adenopathy, immune-mediated glomerulo nephritis, leucopenia, bahvioral abnormalities	Several months
FAIDS	Above symptoms more opportunistic infections, clinical symptoms of immunodeficiency, neoplasia, neurological abnormalities and seizures.	Several months

Table 1. Stages of clinical sings of FIV infection.

Figure 2. FIV infected cats. (Courtesy Bruno Teixeira, Universidade São Paulo, USP).

Figure 3. Stomatitis and gingivitis. (Courtesy Bruno Teixeira, Universidade São Paulo, USP).

Pathologic abnormalities described in FIV positive cats with alterations in the morphology of lymph node: hyperplastic during acute phase, follicular involution in the terminal phase of infection; thymus: cortical involution, atrophy, lymphoid follicular hyperplasia and germinal center formation; intestinal tract: villous blunting, pyogranulomatous colitis, lymphoplasmacytic stomatitis; liver: periportal hepatitis; bone marrow: dysplastic changes, granulocytic hyperplasia and the formation of marrow lymphoid aggregates; kidney: tubulointerstitial infiltrates, glomerulosclerosis; central nervous system: Perivascular cuffing, gliosis, myelitis, loss and reorganization of neurons, axonal sprouting, vacuolar myelinopathy; lung: interstitial pneumonitis, alveolitis; skeletal muscle: lymphocytic myositis, myofiber necrosis, perivascular cuffing; reproductive failure occurs in FIV infected cats (Sellon e Hartmann, 2006; Gunn-Moore & Reed, 2011; Hartmann, 2011).

2.3. Diagnosis and management of FIV-infected cats

The methods used currently for detection of FIV infection in domestic cats include virus isolation, immunological tests for detection of specific antibodies and molecular tests for detection of viral genomic sequences, associated with the clinical diagnosis. Virus isolation is a reliable diagnostic method but is laborious and not used routinely.

The preferred initial tests are ELISA or immunochromatographic test, which detect antibodies recognizing viral structural proteins (such as the capsid protein p24 and a gp41 peptide) and offer the advantage of speed and convenience. However, when the results are inconclusive by these tests a more specific test should be used, such as the Western blot (Hosie et al., 2009). The PCR can have doubtful results due to the great genetic variability of FIV, use of specific primers only for one subtype, low viral load during a long period of infection, and inadequate preparation of PCR components. The specificity and sensitivity of PCR may vary from 40-100% according to the methodology and standardization of the laboratory (House & Jarret, 1990; Hartmann et al., 2007; Hosie et al., 2009). There is also a technique of lymphocytes, for the visualization of CD4⁺/CD8⁺, however, due to the complexity of these tests are not used routinely.

The cats positive for FIV should not be euthanized based only on a positive test result for FIV. These animals have a long life as large as that of uninfected cats, however, should be subject to regular veterinary (at least every 6 months) queries including monitoring biochemistry, hematological, and weight routine, however, the euthanasia should be considered when the clinical problems relate to an advanced stage of FIV infection leading the animal to a poor living conditions.

However, it is important to isolate the animal infected with FIV from others non-infected, and maintain a good state of health of the animal infected, because other conditions can lead to the progression of immune deficiency. Positive cats should be neutered to reduce aggressive and laughter of contamination during fighting and copulation.

Vaccination is a controversial subject. Vaccines with inactivated viruses are available in the U.S.A, Australia, New Zealand and Japan. These vaccines induce a rapid humoral response with antibodies indistinguishable from natural infection. However, there are several studies aimed at differential tests to identify natural FIV infected animals from those vaccinated ones.

Early diagnosis is very important because it will enable early treatment of disease. There are treatments with corticosteroids and other immunosuppressive drugs in animals with chronic stomatitis, however, they cause many side effects. The Filgastrim (granulocyte colony-stimulation factor), a recombinant human cytokine (rHuG-CSF), has been used in cats with profound neutropenia, to increase the neutrophil count, however, can also increase the viral load. The recombinant human erythropoietin is also used successfully in cats with non-regenerative anemia, administration elevates blood cells, without increasing the viral load. Treatment with insulin-like growth factor-1 recombinant human induces thymic growth and stimulates T cell function, resulting in a significant increase in thymus size and

thymic cortical regeneration, replenishing the peripheral T cell pool in experimentally FIV-infected cats (Hosie et al., 2009; Mohammadi & Bienzle, 2012).

Most of the antiviral drug for FIV is licensed for the treatment of HIV infections in humans, with AZT (3'-azido-2',3'-dideoxythymidine), however, many human antiviral, are ineffective or toxic to cats. AZT (3'-azido-2',3'-dideoxythymidine) is a nucleoside analogue (thymidine derivative) that blocks the retroviral reverse transcriptase and inhibits the replication of FIV in vivo and in vitro. As with HIV, FIV resistance may arise after 6 months of treatment (Hosie et al., 2009; Doménech et al., 2011; Mohammadi & Bienzle, 2012).

Some studies have shown promising results with the use of recombinant interferon for the treatment of FIV, increasing the survival of infected animals. Immunomodulators and interferon inducers are most utilized in infected animals, but there are controversies regarding the use, for nonspecific stimulation of the immune system, can also assist in an increase in viral load.

3. Human immunodeficiency virus type 1 (HIV-1) x Feline immunodeficiency virus (FIV)

Like the HIV, FIV belongs to the genus *Lentivirus* of the Retroviridae family. Since the discovery of human immunodeficiency virus type 1 (HIV-1) in 1982 there is an urgent need for animal models to study the pathogenesis of HIV-1 infection and possibilities for interventional strategies (Elder et al., 2008). FIV was described in 1987, and since then, FIV has been proposed as a model for HIV studies, because, among non-primate vertebrates, FIV infection in the cat may be the closest model of HIV infection and acquired immunodeficiency syndrome (AIDS).

FIV is phylogenetically (though not antigenically) related to HIV-1. FIV and HIV share many features in their genomes in comprising three major open reading frames (ORF), gag, pol and env, especially in the pol gene and FIV also has a very similar life cycle to that of HIV (Table 2) (Savarino et al., 2007; Elder et al., 2008; Elder et al., 2010).

	FIV	HIV
Viral genes encoded		
Gag,Pol,Env,LTRs	Yes	Yes
Vif	Yes	Yes
Ver	Yes	Yes
Tat	No	Yes
Vpr	No	Yes
Vpu	No	Yes
OrfA	Yes	No
DU	Yes	No
Nef	No	Yes

Table 2. Comparative viral genes encoded. Modified from Elder et al., 2010.

The similarities and discrepancies in the physiopathology of feline and human viruses in their respective natural hosts presents striking analogies, and several intriguing differences (Tables 3 and 4). FIV and HIV share a common pattern on clinical signs, having initially a nonspecific acute phase, followed by an asymptomatic phase and a phase in which the immune system is compromised and the animal is subjected to secondary infections (Sellon e Hartmann, 2006; Gunn-Moore & Reed, 2011; Hartmann, 1998; Hartamann, 2011; Magden et al., 2011; O'Brien et al., 2012).

The dynamics of infection by FIV and HIV in their natural hosts are very similar, like HIV, FIV can be transmitted via mucosal exposure, blood transfer, and vertically via prenatal and postnatal routes, but FIV is principally transmitted through biting, while natural transmission of HIV occurs mainly via mucosal routes.

The development of disease and clinical signs are also similar in human and cat (Fig. 1 and Table 3), both virus preferentially infects CD4 + T cells, while the cell surface receptors CD4 and CD134 are used for HIV and FIV, respectively, differ: the SU glycoprotein of FIV initially binds to CD134, triggering the conformational changes in SU that allow subsequent interaction between SU and the receptor CXCR4 (Grant et al., 2009). While some viruses arising in the later stages of HIV infections are able to use CXCR4, most natural isolates of HIV use a different chemokine receptor, CCR5. Nevertheless, since CCR5 and CD134 in humans and cats, respectively, are predominantly expressed on CD4+ T cells (Table 4) (Willet et al., 2006a; Grant et al., 2009; Elder et al., 2010).

	FIV	HIV
Oral lesions	Yes	Yes
Lymphadenopathy	Yes	Yes
Neutropenia	Yes	Yes
CD4 T cell depletion	Yes	Yes
Hypergammaglobulinemia	Yes	Yes
Wasting, diarrhea	Yes	Yes
Secondary infections	Yes	Yes
CNS lesions	Yes	Yes
Neoplasia	Yes	Yes

Table 3. Comparative disease symptoms. Modified from Elder et al., 2010.

Host immune response against FIV in domestic cats is very similar to those induced in HIV-infected patients. Both viruses cause dysfunction of the CD4+ lymphocyte early in infection, although FIV also infects the CD8+ subset, B lymphocytes and macrophages and ultimately cause immune system collapse. Epitopes recognized by humoral and cytotoxic cellular immune responses have been described in both *Env* and *Gag* genes. Some studies suggest that progression to AIDS may be associated with a TH2-type response, while resistance may be higher in individuals with a strong TH1-type response.

The evaluation of vaccine strategies in animal models is essential to instruct development of a vaccine against HIV. Currently, there are studies using transgenic cats expressing HIV

proteins, serving as valuable models to study the pathophysiology of HIV. A vaccine against FIV, whose development has been the object of considerable international research effort, has intrinsic value as well as the potential to provide a powerful proof of concept in vaccination against human AIDS (Klonjowski et al., 2009).

	FIV	HIV
Transmission		
Blood contact	Yes	Yes
Mucosal contact	Yes	Yes
Vertically via prenatal	Yes	Yes
Postnatal routes	Yes	Yes
Target cell		
CD4+ T cell	Yes	Yes
Macrophage	Yes	Yes
Dendritic cell	Yes	Yes
Subset B cells	Yes	?
Microglia	Yes	Yes
Receptors utilized		
CD4	No	Yes
CD134	Yes	No
CXCR4	Yes	Yes
CCR5	No	Yes

Table 4. Comparative properties of FIV and HIV. Modified from Elder et al., 2010.

4. Feline leukemia virus

Feline leukemia virus has been reported mainly in domestic cats and, was first described in 1964 by William Jarret and co-workers. It is considered more pathogenic than FIV and FeLV infection has higher impact on mortality, because causes more severe immunosuppression than that caused by FIV infection (Hartmann, 2006; Lutz et al., 2009).

The FeLV genome contains envelope (*env*), polymerase (*pol*) e group specific antigen (*gag*) genes that encode for the surface (SU) protein glycoprotein gp70 and the transmembrane (TM) protein p15E; reverse transcriptase, protease and integrase; internal virion proteins, including p15c, p12, p27 and p10; respectively. The p27, which is used for clinical detection of FeLV and gp70 defines the virus subgroup (Hartmann, 2006; Lutz et al., 2009).

Although it has not been described serotypes for FeLV virus isolates have variants or subgroups (FeLV-A, FeLV-B, FeLV-C and FeLV-T). These subgroups are distinguished by the nucleotide sequence of the *env* gene and, antigenically they are closely related. Variations in protein SU sequences would be responsible for use by the virus of different cell receptors, resulting in differences in tropism including bone marrow, salivary glands and respiratory epithelium, and pathogenicity of field isolates (Neil et al., 1991; Roy-Burman et

al., 1995). Subtype A is more disseminated, it is involved in all clinical infections and is related to immunodeficiency. Only FeLV A is contagious and passed horizontally from cat to cat in nature. The host cell receptor used by FeLV is *Feline highaffinity thiamine transporter 1* (feTHTR1), found in absorption tissues and small intestine besides liver and kidneys, and also in cells of the lymphoid system. This wide distribution is consistent with the fact that the FeLV-A is found in a variety of tissues and cells and this subgroup can cause lymphomas, but usually causes injury moderate in the absence of other subgroups. Subtype B originates from recombination of FeLV-A is primarily associated with tumors. Subtype C considered the most pathogenic subgroup, emerges from mutations in the *env* gene of subtype A and is mainly associated with non-regenerative anemia. Subtype T was originally isolated from a cat with FeLV induced immunodeficiency (FAIDS). This subgroup arises from mutations in the SU gene sequence of the FeLV-A with approximately 96% similarity. It is defined by its T lymphotropism. This subgroup requires a membrane-spanning receptor molecule (PIT1) and a co-receptor protein (FeLIX) to infect T lymphocytes and causes usually severe immunosuppression. In fact, all naturally infected cats carry FeLV A either alone or in combination with FeLV B, FeLV C, or both (Neil et al., 1991; Roy-Burman et al., 1995; Hartmann, 2006; Lutz et al., 2009).

4.1. Epidemiology and transmission

The feline leukemia virus has a worldwide distribution. FeLV is contagious and spreads through close contact between viral shedding, but the prevalence of infection varies greatly depending on their age, health, environment, density of animals and lifestyle (Hard et al., 1976; Grant et al., 1980). The kittens are more susceptible, since the resistance develops with age. Because of advances in the diagnosis of disease and vaccination the prevalence of FeLV has dropped substantially in the last two decades. In Shelters and places where there is a high density of animals, it is advisable to proceed diagnosis of all animals. Infected animals should be euthanized or isolated from not infected animals.

FeLV is transmitted mainly by oronasal contact, through saliva, urine, feces, ingestion of contaminated food and water and also through bites. Transmission can also take place from an infected mother cat to her kittens, either before they are born or while they are nursing. Older cats are more resistant to FeLV infection, but can be infected by high viral doses (Lutz et al., 2009).

4.2. Pathogenesis, immunity and clinical symptoms

FeLV is present in the blood during two different stages of infection: primary viremia, an early stage of virus infection. During early stage some cats are able to mount an effective immune response, eliminate the virus from the bloodstream. The second stage is characterized by persistent infection of the bone marrow and other tissues (Table 5) (Hard et al., 1976; Hartmann, 2006; Fugino et al., 2008). If FeLV infection progresses to this stage it has passed a point of no return: the overwhelming majority of cats with secondary viremia

will be infected for the remainder of their lives. The pathogenesis of FeLV is different in each cat and depends on immune status and age, but can be classified into six stages (Table 6) (Hard et al., 1976; Charreyre & Pedersen, 1991; Hartmann, 2006; Fugino et al., 2008; Lutz, 2009).

Classification of evolution of the disease	Classification of infected animals	Response immune	Days after infection	Healthy cat
Regressive infection extinct	Transient viremia	Efficient - virus neutralization	Days	FeLV negative - Animal resistant future infections for a period of time
Progressive	Persistent viremia	Failure to develop an immune response effective	3 weeks	FeLV positive
Regressive	Latent infection	Body inactive the virus, but not neutralizes	3-13 weeks	FeLV negative (complete elimination) FeLV positive (continued viremia)
Atypical		Complete virus is sequestered in the epithelial tissue, replicates itself, but leaves the cells	3-13 weeks	FeLV positive

Table 5. Immune responses following infection. Modified from Hartmann, 2006.

Clinical signs associated with FeLV infection are variable (Fig. 4). It has seen tumors in infected cats once FeLV is a major oncogene that causes different kind of tumors, most commonly malignant lymphoma and leukemia and other hematopoietic tumors. It also induces thymic atrophy and depletion of lymph node paracortical zones following infection. Besides that it has been found immunosuppression with poor response to T-cell mitogens, reduced immunoglobulin production; hematologic disorders like lymphopenia and neutropenia; immune-mediated diseases; neuropathy; reproductive disorders; fading kitten syndrome and opportunistic infections. The lymphopenia may be characterized by preferential loss of CD4⁺/CD8⁺ ratio and losses of helper cells and cytotoxic suppressor cells and primary and secondary humoral antibody responses are delayed and decreased (Hartmann, 2006; Lutz et al., 2009; Hartmann, 2011).

FeLV infected cats having concurrent protozoal, bacterial, viral, and fungal infections, most commonly bartonellosis, respiratory infections and coccidiosis (Wolf-Jäckel et al., 2012; Sobrinho et al., 2012). Diseases such as hemolytic anemia, glomerulonephritis, chronic enteritis with intestinal epithelial cell degeneration and necrosis of the crypts, liver disease, reabsorption fetal, abortion, stillbirth, lymphadenopathy, polyarthritis and neurological

diseases such as peripheral neuropathies, may be related to FeLV infection (Hartmann, 2006; Lutz et al., 2009; Hartmann, 2011).

Stages	Replication region	Pathogenesis	Days post infection
I	Oropharynx and lymph nodes	Infects lymphocytes, which travel to the bone marrow	2- 12 days
II	Lymphocytes and monocytes	Immune suppression, thymic atrophy, lymphopenia, neutropenia, neutrophil function abnormalities, loss of CD4 ⁺ cells and CD8 ⁺ lymphocytes	2- 12 days
III	Systemic lymphoid centers	Immune suppression	2- 12 days
IV	Bone marrow cells and epithelial cell	Anaemia and lymphoma	2- 6 weeks
V	Bone marrow stem cells	Myelosuppression and leukemia	4- 6 weeks
VI	Viremia medullary epithelial and lymphoid	Thrombocytopenia and neutropenia	4- 6 weeks

Table 6. Stages of replication of the virus of feline leukemia (FeLV).

Figure 4. Gingivitis. (Courtesy Marcia Moller Nogueira).

The feline oncovirus associated-membrane antigens (FOCMA) may be associated with immunodeficiency that occurs because of depletion of lymphoid cells infected, probably due to antibody-mediated cytotoxic. Leukemia and anemia are induced by the transformation of stem cells, myeloid and lymphoid lineages, induced by infection with FeLV (Hard et al., 1976; Lutz et al., 2009; Hartmann, 2011).

4.3. Diagnosis and management of FeLV-infected cats

The correct and early diagnosis is important for prevention and control of FeLV infection. Diagnostic tests detect antigens and, cats of any age should be tested. For the diagnosis of FeLV, virus isolation is not widely used, because it is difficult, time consuming to perform and requires special facilities, though viral antigens could be detected in peripheral blood cells, this method has been considered as the ultimate diagnostic criterion. Most often, the diagnosis of infection is done based on clinical history and detection of antigens, the FeLV core protein (p27), in leukocytes, plasma, serum or saliva of suspected animals (Barr, 1998; Hartmann, 2006). The direct immunofluorescence assay in blood smears, is the most commonly used diagnostic methods for detection of the virus, targeting mainly proteins p27 and p55 that are present in infected leukocytes (Hard, 1991). Tests such as ELISA and immunochromatography for the p27 protein have high sensitivity and specificity and are preferred used because they are less laborious, however, when doubtful results occurs it should be confirmed by direct immunofluorescence (Table 7) (Hard, 1991, Hartmann et al., 2007; Lutz et al., 2009). PCR is being used currently for detection of viral nucleic acid (RNA or proviral DNA) and is highly strain specific. PCR positive for FeLV proviral DNA indicates the presence of exogenous but not necessarily can be used as a diagnosis for viremia (Gomes-Keller et al., 2006). In these cases the RT-PCR detects the presence of viral RNA and informs the development of viremia in infected animals, but current reagents and testing protocols should be well standardized. As a retrovirus, mutations in FeLV occur naturally and may react negatively with a specific PCR.

It is necessary a good classification of the stage (Table 6) of the disease to obtain an accurate diagnosis. In phases I-III only ELISA can detect viral antigens for FeLV, and in the stages IV-VI can be detected by ELISA, immunofluorescence and PCR. The combination of testing determines the FeLV infection status of most cats. Recommend annual retesting after any discordant test result until agreement. A positive test doubtful a healthy animal, it should be done further confirmatory tests such as direct immunofluorescence and PCR for provirus (Gomes-Keller et al., 2006; Hartmann, 2006; Lutz et al., 2009).

For an accurate diagnosis, it is also necessary to evaluate the age and lifestyle of the animal (Table 7): Negative animals under 12 weeks who had contact with sick birds or other animals should be retested within 4-6 weeks; positive results indicate that at this age the animals are infected. Negative animals with more than 12 weeks who had contact with sick birds or other animals should be retested within 6-8 weeks; positive results at this age should be classified as follows: sick animals (positive), healthy animals, retesting within 6-8 weeks.

The early and precise diagnosis is needed to enable rapid intervention. FeLV-infected cats should be isolated from uninfected ones. It is also recommended that they could be examined by the vet regularly (every 6 months), doing biochemical tests, complete blood count and urinalysis. Infected animals should be sterilized to minimize the transmission. The living environment should be cleaned periodically, because FeLV is sensitive to any type of disinfectant.

Age	Result of the diagnosis	Lifestyle of the animal	Interpretation	Measure
Less than 12 weeks	Negative	Kept contact with other animals and /or sick animals	Re-test after 4-6 weeks	The result of the last test will be conclusive
		Not kept contact with other animals and / or sick animals	Uninfected	
	Positive	Even that has ingested colostrum positive for FeLV	Infected	Isolation of animal and clinical control every six months.
More than 12 weeks	Negative	Animal exposed to sick or diseased animals	Re-test after 6-8 weeks	The result of the last test will be conclusive
		Animal no manifestations	Uninfected	
	Positive	Sick animal	Infected	
		Animal health	Re-test after 6-8 weeks	The result of the last test will be conclusive

Table 7. Interpretation of results obtained by ELISA and direct immunofluorescence. Modified from Hartmann, 2006.

As immunomodulatory therapy are used to good clinical improvement, but are still under study. Antivirals such as AZT that acts effectively against FeLV replication in vitro and in vivo reducing the viral load, improving the immune response and clinical condition of the animal (Cotter, 1991; Hartmann, 2006; Lutz et al., 2009). Infected animals should be treated for other infections promptly to prevent an impaired immune system and should be vaccinated regularly against other pathogens like rabies virus, feline panleukopenia, rhinotracheitis, calicivirus, chlamydiosis and other (Cotter, 1991; McCaw, 1995, Lutz et al., 2009). Corticosteroids should be avoided, but if stomatitis or gingivitis occurs they can be used to facilitate the intake of food. In cats with anemia, blood transfusions may be useful and leukopenia can be treated with colony-stimulating factors (Cotter, 1991; McCaw, 1995, Lutz et al., 2009).

All animals should be tested for FeLV and thereafter be vaccinated at the age of 8-9 weeks and again at 12 weeks with annual boosters. Older animals are less susceptible to infection

and can be vaccinated at intervals of 2-3 years. Vaccines prepared with inactivated whole virus obtained from cell cultures are available commercially, as well as vaccines containing recombinant viral proteins expressed in heterologous systems. No FeLV vaccine provides 100% efficacy of protection for FeLV and none prevents infection, but vaccination offers good prevention of fatal cases. The immunization of animals with inactivated vaccines may result in a reduction of 70% incidence of the disease. FeLV immunization should be part of the routine vaccination programmed for pet cats. However, the most effective way to prevent the spread of infection is testing for FeLV and preventing exposure of healthy cats to FeLV infected cats (Cotter, 1991; McCaw, 1995, Hartmann, 2006; Lutz et al., 2009).

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