Clinical and Pathological Features Associated with Feline Immunodeficiency Virus Infection in Cats

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Feline immunodeficiency virus (FIV) is a member of the lentivirus subfamily of retroviruses. This group of viruses, which includes the human and simian immunodeficiency viruses (HIV and SIV) derive their name from the typically slow time course of the infections they cause.[15] FIV is a typical lentivirus with respect to gross and structural morphology. The viral genome is composed of single-stranded RNA which is transcribed into double-stranded RNA which is transcribed into double-stranded DNA using a Mg^{2+} dependent reverse transcriptase enzyme. The viral DNA is then inserted into the genome of the infected host cell and is replicated whenever the host cell divides.[18, 21] Lentiviruses are known for persistent viral infections within mononuclear cells, often in the face of a strong host immune response.[15]

FIV was first isolated in 1986 from a group of cats in Petaluma, California. The discovery was prompted by an outbreak of an acquired immunodeficiency syndrome (AIDS) like disease among a group of feline leukemia virus (FeLV) negative cattery animals.[18] Since initial isolation, identical virus has been isolated from cats in all 50 of the United States, Canada, Europe and Japan. FIV appears to be endemic in these cat populations rather than epidemic. This and the widespread nature of the infection suggests that the virus had been in the cat population for a long time prior to being isolated.[19] All isolates of FIV have been recovered from domestic cats, however, serum samples from several species of wild *Felidae* have been found to contain anti-bodies that react strongly to FIV antigens. Attempts to isolate a lentivirus from seropositive wild cats have been unsuccessful.[2]

Epidemiology

Animal lentivirus infections such as FIV are transmitted between animals primarily by cell-associated virus within macrophages or monocytes.[19] Virus has been recovered from blood, serum, plasma, cerebrospinal fluid, and saliva of infected cats. Expanded sero-epidemiological and experimental studies have demonstrated that the most common and efficient mode of FIV transmission is by bite. Cats with clinical signs of illness tend to have higher virus loads in their saliva than clinically normal animals and a single experimentally administered bite from an infected cat will transmit the virus to a susceptible animal.[30]

Territorial aggression and biting support the epidemiologic features of FIV infection in feral and indoor-outdoor cat populations. The highest prevalence of infection (1-12%) is found in populations of free-roaming cats. Male cats are twice as likely to become infected than female cats and have a mean age at presentation of 5-6 years. Prevalence is lowest in closed, purebred catteries where aggression among familiar animals is limited.[19]

Close, intimate contact between animals such as grooming and shared use of litter pans and foodbowls is not a documented means of spreading infection. Venereal transmission from infected toms to non-infected queens or from infected queens to non-infected toms cannot be experimentally reproduced.[19] Experimental studies have demonstrated that FIV can be transferred from infected queen to kittens, however, the exact mode of transmission has not been determined. Possible means of spread of infection include *in utero* transmission, infection during parturition, or transmission postnatally by lactogenic or salivary secretions.[28]

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Clinical Syndrome

Lentiviruses like FIV, SIV, and HIV share a common disease pattern consisting of three sequential stages or disease states: first, an initial primary stage of infection; second, an asymptomatic carrier (AC) stage and third, a secondary or AIDS-like stage of infection.[3,19] The initial or primary stage of infection has been well characterized by experimental infection of specific pathogen free (SPF) cats.[3,5,8,14, 17,19,21,30.] The primary stage of FIV infection is manifest as a transient, acute, flu-like illness. Infected animals appear outwardly normal until approximately 10 days post-infection (PI). At this time generalized lymphadenopathy is often the first noticeable sign with nodes palpably enlarged 1-10 times the normal size. Acute, flu-like disease develops 4-8 weeks PI. Clinical signs may include fever, diarrhea, depression, dehydration, mild respiratory disease, dullness, anorexia, weight loss, soreness and stiffness. Variable ocular signs including conjunctivitis, anterior uveitis and photophobia may also be present.

Clinical signs of the acute phase last for up to 40 weeks then diminish as the AC stage is entered. Most infected animals recover from the acute phase of the disease to become lifelong carriers of the virus. Complete recovery with removal of the virus from the body does not appear to occur to any extent in nature or in the laboratory setting.[17,19]

Disease course and progression of infected animals to the secondary stage of infection is less predictable than the course of the primary stage of FIV infection. Naturally infected cats and experimentally infected random source (RS) animals develop an AIDS-like syndrome with more predictability than experimentally infected specific pathogen free (SPF) cats. AIDS-like disease can be reproduced in SPF cats using the Japanese strain of FIV, however, naturally infected animals and animals in high disease exposure environments that die of terminal disease invariably have more severe opportunistic infections (cryptococcosis, toxoplasmosis, hemobartonellosis, and atypical mycobacteriosis) when compared to FIV-infected SPF animals. It is believed that cofactors play an essential role in the development of clinical disease possibly by providing concurrent opportunistic infections and stimulation of cytokines that lead to virus replication. Disease course may also reflect the age at inoculation and immunologic background of the individual.[17,19]

The time interval from infection to the development of the AIDS-like stage can range from 6 months to more than three years PI. Clinical manifestations of terminal FIV infection are highly variable often reflecting the presence of progressive secondary opportunistic infections of the oral cavity, upper respiratory tract, gastrointestinal tract, urinary tract, and skin. Other animals may suffer more vague signs of illness reflective of underlying hematologic abnormalities, neoplasms, or neurologic disease.[19]

The majority of clinically affected cats (50%) will present with chronic infections of the mouth including gingivitis, stomatitis, or periodontitis. About one-fourth of FIV infected cats will present with chronic infections of the upper respiratory tract, nasal passages or conjunctiva of the eyes. Another 15% of infected cats will present with chronic infections of the skin or external ear canals (Staphylococcus) or with generalized mite infections (Demodectic or Notoedric mange). Chronic enteritis manifesting as diarrhea or weight loss is the presenting sign for around 10% of infected cats. An additional one-third of infected cats are presented to the veterinarian for vague signs of illness such as fever, anorexia or neurologic signs. Neurologic signs are representative of cortical involvement and may include behavior changes, dementia, twitching, movements of the face and tongue, loss of litter box training, compulsive roaming, seizures or aggression. Ocular signs including focal retinal degeneration, herpetic keratitis, or retinopathy may also be presented.[11,19]

Virus Dissemination

Using polymerase chain reaction techniques it has been determined that an early peak viremia immediately preceeds the onset of acute phase symptoms in infected cats. Virus levels remain high throughout the symptomatic phase of the infection then decline as clinical signs resolve and the AC stage is entered.[6] Early virus dissemination of FIV in the acute phase of the disease is to both lymphoid and non-lymphoid organs. During the primary stage of virus infection, both tissue types often contain heavy loads of FIV-infected cells.[5,17] The majority of infected cells are in the lymphoid organs and the germinal centers harbor many of these cells. The thymic cortex is also a major site of early infection.[3] Prior to the onset of the acute disease, T-lymphocytes are the primary cellular targets, however, there is a shift in cellular targets to macrophages with the development of the acute syndrome. It is believed that this early shift in the cellular targets of FIV may be important in the maintenance of persistent FIV infection.[3] In the chronic stages of the disease, FIV antigen can be demonstrated within macrophages in lymph nodes and in peripheral blood mononuclear cells.[17] Virus

has also been recovered from CSF, cerebellum, mid-brain and brainstem. [22]

Hematological Abnormalities

FIV-infected cats often show abnormalities in their hemograms. Development of hematologic abnormalities coincides with the onset of the acute disease syndrome. The most common finding in the acute stage of FIV infection in SPF cats is a leukopenia occurring 4-8 weeks PI. The leukopenia is initially associated with a mild lymphopenia but later by an absolute neutropenia of variable severity.[1,3,5,8,19,30.] The leukopenia is usually transient lasting 2-4 weeks with leukocyte numbers returning to near pre-infection levels as normal health returns and the AC state is reached. However, after recovery from the primary stage of infection, FIV-infected cats as a group tend to have significantly decreased absolute neutrophil counts when compared to non-infected cats.[21]

The development of the AIDS-like phase of FIV infection is heralded by the reappearance of hematologic abnormalities. The severity of these abnormalities increases with the duration and severity of the clinical disease state. Cytopenias including anemia, neutropenia, lymphopenia, and thrombocytopenia are the most common findings in FIV-infected cats manifesting clinical signs of disease. One-half to two-thirds of clinically ill cats show some degree of leukopenia and/or anemia.[4,18,19,30] The anemia can be regenerative or non-regenerative with the latter being associated with concurrent myeloid dysplasia or myeloproliferative disorders. Multiple cytopenias are also common.[24,30]

Immunologic Abnormalities

Significant changes in immunologic parameters are seen in both the acute and chronic phases of FIV infection. As early as 6 weeks PI, a panT-cell lymphopenia can be observed. CD8+T-cells subsequently return to pre-infection or above pre-infection levels, however CD4+T-cell numbers fail to return to normal values. This results in persistently decreased numbers of CD4+ lymphocytes and a concomitant decrease or inversion of the CD4+/CD8+ T-lymphocyte ratio. CD8+T-cell and B-cell distribution are not significantly altered.[3,11,22,26,27] The decrease in T-cell ratio continues throughout the acute phase of infection reaching a nadir at around 8-10 weeks PI. The rapid decrease in CD4+ T-cells that occurs with primary acute disease is greatly slowed during the subsequent asymptomatic stage of the infection. At this time, significant immunologic abnormalities persist although infected animals appear outwardly healthy with no signs of immunodeficiency evident.[8]

Inversion of the CD4+/CD8+ T-cell ratio persists in chronically infected cats. CD8+ T-cell numbers remain high until just before the development of clinical disease when CD8+ cell numbers begin to decline.[11] With natural infection, or in random source (RS) animals experimentally infected with FIV, hyperglobulinemia is often seen. Serum levels of IgG are significantly elevated while levels of IgM and IgA remain normal indicating B-cell activation during chronic FIV infection. This also suggests a role for infectious cofactors since B-cell responses were not altered in FIV-infected SPF cats.[1,5,11]

T-cell responses are altered in both RS and SPF cats. Gradual, significant decreases in mitogen response to T-cell-dependent immunogens appear around the same time that the AIDS-like disease develops. Lymphoproliferative responses to pokeweed mitogen and concanavalin A were both diminished in chronically infected cats. The ability of B-cells to recognize and respond to T-cell-independent immunogens is not altered by FIV infection.[11,26]

Pathologic Features

Gross pathologic changes in the primary, acute stage of FIV infection are limited to changes in lymph nodes. Generalized lymphadenomegaly involving peripheral and visceral lymph nodes is commonly observed. Nodes are uniformly enlarged with distinct cortical and medullary differentiation being preserved.[3,5]

Histologically, the most striking changes in the primary stage of infection are associated with the peripheral lymphoid organs including lymph nodes, spleen, and mucosa-associated lymphoid tissues. Lesions consist of progressive hyperplastic changes seen as increased number and/or size of lymphoid follicles and prominent, mis-shapen germinal center formation. Lymphoid hyperplasia is the result of expansion of both B-cell and T-cell regions of the peripheral lymphoid organs.[3,5,8] Changes are also present in central lymphoid organs including thymic cortical involution with loss of cortical thymocytes, and follicular hyperplasia of the thymic medulla, bone marrow and parathyroids.[3,5,8] The magnitude of these changes increases with time post-infection.

Histopathologic lesions are also encountered in non-lymphoid organs during primary infection. Commonly these are inflammatory diseases observed as

trans-mural typhilitis and pulmonary and renal interstitial inflammatory infiltrates predominantly of a histiocytic nature. Central nervous system lesions are characterized by vascular and perivascular inflammatory infiltrates of histiocytes and lymphocytes, glial nodules and diffuse gliosis.[3,7,8,14]

Gross pathologic changes in the chronic stages of infection are present in non-lymphoid and lymphoid tissues. Changes in non-lymphoid tissues reflect the clinical presentation of the animal and the types of opportunistic infections present. Lesions are typically inflammatory changes, involving intestines, brain, lung, liver, kidneys, and the oral cavity.[3,4,7,8,11,14]

Other gross lesions include wasting, severe dehydration, poor haircoat, skeletal muscle atrophy and occasionally lymphosarcoma.[5,17] Aggregates of lymphoid cells can be found within salivary glands, kidney, and in the sclera and choroid of the eye.[5] Perivascular cuffing and glial nodules in the brain are also seen in the secondary stages of infection.[22]

The most consistent gross pathologic findings in the chronic stages of infection are in the lymphoid tissues. Lymph node changes range from enlargement to atrophy depending on the location of the node. Lymph node draining sites of chronic inflammation tend to be enlarged.[4] Histologic lesions in lymphoid tissues reflect three patterns of change: one, follicular hyperplasia; two, follicular involution; and three, a combination of follicular hyperplasia and involution within the same node. These lymph node changes are not diagnostic for lentivirus-associated immunodeficiency since similar changes can be seen in clinically normal animals. These changes most likely represent a continuum in the disease process and may have prognostic significance, as once the AIDS-like disease state is reached, the nodes are consistently involuted.[1,7,23]

Conclusion

FIV infection in domestic cats provides an ideal model for the study of HIV infection in humans. The disease produced is similar as well as is the temporal progression of the clinical signs. FIV does not represent the ideal animal model as an identical virus is not utilized; however, the universal availability of cats and the ability of many research facilities to become equipped to handle them makes FIV a particularly good model. Many aspects of FIV viral kinetics, pathogenesis, immunity, and susceptibility to antiviral agents are very similar to those of HIV, thus supporting the use of this model for the testing of prophylactics and chemotherapeutics.[12,13,14] ∎

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