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Viral Reproductive Pathogens of Dogs and Cats

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Viruses represent a significant cause of reproductive failures in both dogs and cats. Pregnancy losses can be caused by transplacental transmission of virus with direct infection of embryos and fetuses or, less frequently, by severe debilitation of pregnant animals in the absence of congenital infection.[1] In addition to the direct effect on pregnancy, certain viruses, such as the minute virus of canines (MVC), canine herpesvirus (CaHV), and feline panleukopenia virus (FPLV), can cause perinatal infections leading to neonatal mortality or abnormalities.[2–4] This review discusses viral infections that affect canine and feline pregnancy, with particular emphasis on pathologic, diagnostic, and prophylactic features.

CANINE VIRAL REPRODUCTIVE PATHOGENS

Canid Herpesvirus 1

Canid herpesvirus 1 (CaHV-1) is an alphaherpevirus closely related to felid herpesvirus 1, phocid herpesvirus 1, and equid herpesviruses 1 and 4.[5] Only dogs are fully susceptible to CaHV-1 infection and disease, although specific antibodies have been found in wild carnivores worldwide. By serologic investigations, the virus has been shown to be widespread in domestic dog populations, with the highest seroprevalence in kenneled dogs. Virus transmission usually occurs through direct contact with genital or oronasal secretion of infected animals. The clinical course of CaHV-1 infection depends on the age of infected pups, with the fatal, systemic form of disease occurring in puppies less than 2 weeks of age.[3] In fact, CaHV-1 replicates best at temperatures lower than 36°C (96.8°F), which are commonly observed in the first week after birth. Newborn puppies can be infected during passage through the birth

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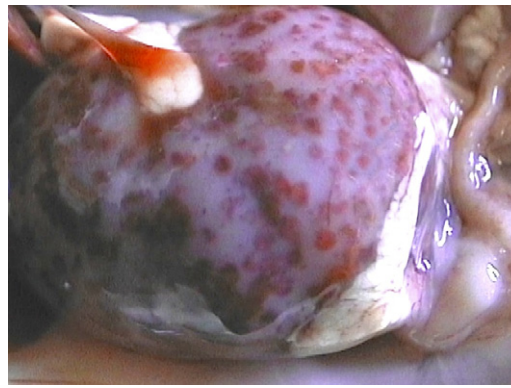

Fig. 1. Puppy with natural neonatal CaHV-1 infection. Multiple renal hemorrhages are evident.

canal or by contact with oronasal secretions of infected animals. CaHV-1–induced generalized disease is characterized by loss of appetite, abdominal pain, soft feces or diarrhea, ataxia, serosanguineous nasal discharge, and mucosal hemorrhages. The death of infected puppies usually occurs at 3 to 7 days after the appearance of clinical signs and may involve an entire litter. Although puppies older than 2 weeks usually develop subclinical disease, neurologic disorders have been associated to CaHV-1 infection.[6]

In neonates that die as a consequence of systemic infections, postmortem findings are pathognomonic, consisting of scattered hemorrhages within the kidney (**Fig. 1**), multifocal areas of necrosis in the liver and lungs, and enlargement of spleen and lymph nodes. Histologically, the prevalent lesions are represented by foci of hemorrhage and necrosis with eosinophilic intranuclear viral inclusions in parenchymatous organs.[7]

CaHV-1 is uncommonly associated with transplacental infections, leading to fetal or neonatal death. The effects of in utero infection depend of the age of gestation when infection occurs. Bitches infected at mid-gestation may abort or deliver stillborn puppies in the absence of other clinical signs including vaginal discharge. Some puppies may appear normal but develop the systemic form within few days after birth.[8] After in utero infection, multifocal necrotizing lesions are evident in the placentas, whereas findings in aborted fetuses are similar to those observed in the systemic neonatal form. The uterus of infected bitches may contain dead fetuses of varied sizes (**Fig. 2**).

In adult dogs, CaHV-1 is believed to be responsible for infectious tracheobronchitis, but it has not proved to be a primary agent. Canine infectious respiratory disease (CIRD) is multifactorial and may be caused by several viruses (CaHV-1, canine adenoviruses, canine coronavirus, canine distemper virus, canine parainfluenza virus, canine influenza virus) and bacteria (*Bordetella bronchispetica*, *Mycoplasma* spp, *Streptococcus* spp).[9] However, sexually mature dogs may develop venereal infections characterized by lymphofollicular (**Fig. 3**) and/or papulovesicular lesions and hyperemia of the genital tract.

Gross lesions of puppies affected with CaHV-1 infection are usually diagnostic; histopathology can be performed for confirmation. Diagnosis of CaHV-1 infection can also be obtained by virus isolation on susceptible cell lines of canine origin, immunofluorescence assay on tissue sections or smears, and the polymerase chain reaction (PCR). Recently, a real-time PCR assay, based on the TaqMan technology,

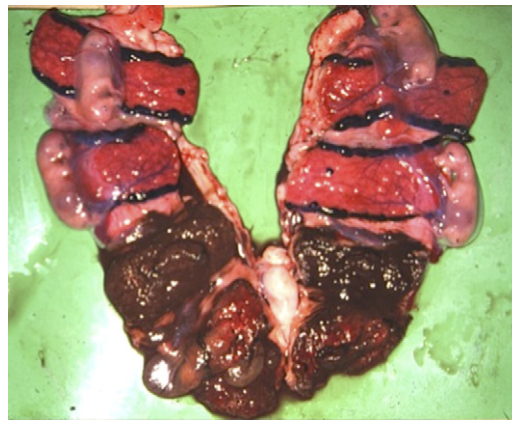

Fig. 2. Uterus of pregnant bitch with experimental CaHV-1 infection. The fetuses are of various sizes and stages of decomposition. (*Courtesy of* Dr A. Hashimoto, Hokkaido University, Japan.)

has been developed for detection and quantification of CaHV-1 DNA.[10] Clinical samples suitable for CaHV-1 diagnosis include kidney or other affected organs from dead neonates or aborted fetuses, nasal and pharyngeal swabs from CIRD-affected dogs, and vaginal or preputial swabs from adult dogs with lesions in the genital tract. Serology, using immunofluorescence or virus neutralization, may help assess virus circulation in kennels and rescue shelters, but it is not the gold standard for diagnosis of active infections due to the propensity of CaHV-1 to establish latency.

To date, there is no effective treatment for CaHV-1 neonatal infections. Experimental elevation of the environmental temperature resulted in suppressed viral replication, but it is ineffective as a treatment.[11] Administration of antiviral drugs (eg, vidarabine or acyclovir) has been shown to be effective against human herpesviruses, but trials

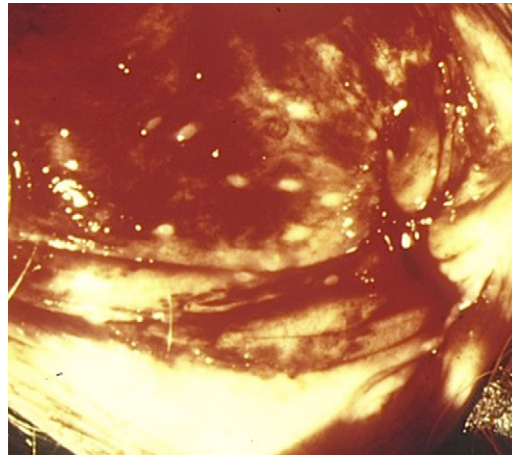

Fig. 3. Bitch with natural CaHV-1 infection. The vaginal mucosa is multifocally hemorrhagic. (*Courtesy of* Dr A. Hashimoto, Hokkaido University, Japan.)

in dogs have not produced conclusive results.[7] CaHV-1 vaccination may be used in breeding kennels with reproductive disorders to immunize bitches before mating in order to protect pregnancy and prevent infection of newborns. In Europe, a subunit vaccine containing CaHV-1 glycoprotein B is available, although its efficacy has been questioned. This vaccine should be administered only to bitches during heat or in the early pregnancy and again at 6 to 7 weeks of gestation.[3]

Canine Minute Virus (Canine Parvovirus 1)

Canine minute virus (CnMV), also known as MVC or canine parvovirus type 1 (CPV-1), was first isolated from the feces of asymptomatic dogs in 1967.[12] CnMV is an autonomous parvovirus genetically and antigenically unrelated to canine parvovirus type 2 (CPV-2), which causes fatal gastroenteritis in young dogs.[13] Recent studies have shown that CnMV is more closely related to bovine parvovirus and human bocaviruses, and now has been included in the new genus *Bocavirus* of the family Parvoviridae.[14] Only dogs have been shown to be susceptible to CnMV infection. Serologic investigations have demonstrated seroprevalences of 5% to 15.4% in Japan, 5.6% in Germany, 11.8% in Korea, 13.6% to 17.6% in Italy, 18% in Turkey, and 30% to 70% in the United States.[4,15]

CnMV infection has been associated with a variety of clinical forms, including asymptomatic infections, respiratory distress, enteric disease, neonatal mortality, and reproductive disorders.[4] The virus has been detected by virus isolation or PCR in the feces of both healthy and diarrheic dogs.[12,16] Experimental infections of puppies of different ages with the original isolate of Binn[12] that had been passaged several times in cell culture failed to reproduce the disease, but the virus was recovered from the feces and internal organs of inoculated pups.[17] In a subsequent experiment with a low-passage CnMV isolate,[18] 5-day-old puppies had severe respiratory, but not enteric disease. Natural outbreaks of CnMV-associated neonatal mortality have been reported.[18–21] Puppies infected at less than 4 weeks of age often had mild or vague symptoms preceding their rapid death; others displayed depression, loss of appetite, acute myocarditis, respiratory distress, and/or enteritis.[4] Virus-induced immunosuppression due to reduction of monocyte phagocytosis may play a role in CnVM pathogenesis.[22]

Analogous to other parvoviruses, CnMV can cause transplacental infections leading to subclinical disease, embryonic resorption, abortion, birth deformities, or neonatal mortality.[4] Different outcomes of CnMV infection in pregnant bitches depend on the time of infection during gestation. Infections during the first half of pregnancy may result in embryo death and resorption (**Fig. 4**), whereas stillbirths and the birth of weak pups are more frequently observed in the late stages of pregnancy.[18] Direct inoculation of fetuses in late gestation resulted in arrested fetal development (**Fig. 5**). Recently, CnMV was reported to be associated with neurologic disease in dogs of various ages[23] and with severe gastroenteritis in an elderly dog.[24]

Postmortem findings in nursing puppies include pneumonia (**Fig. 6**), enteritis, myocarditis, and thymic edema and atrophy. Histopathologically, eosinophilic intranuclear viral inclusions are observed in the epithelial cells of intestinal crypts and in myocardiocytes. Other histologic changes are hyperplasia of the intestinal crypts, necrosis of myocardium, interstitial pneumonia, and lymphocyte depletion in thymus and other lymphoid tissues.[4]

CnMV infection should be taken into account in fetal abnormalities, abortion, and neonatal mortality. Samples for a laboratory diagnosis should consist of fetal or neonatal tissues such as myocardium, intestine, and lungs. CnMV diagnosis is based on virus isolation on Walter Reed canine cells (3873D cells), followed by detection of

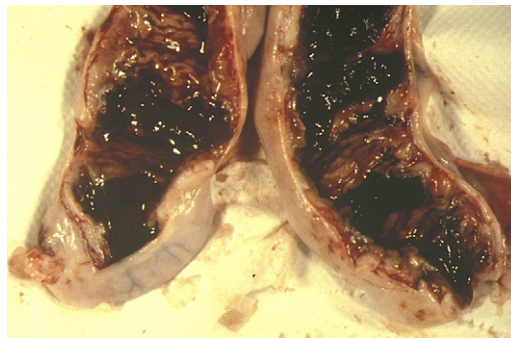

Fig. 4. Uterus from a bitch with experimental CnMV infection (early gestation). There is embryo death, decomposition, and resorption.

intranuclear inclusion bodies by hematoxylin-eosin staining or of viral antigens by immunofluorescence, using specific antibodies. Recently, Madin-Darby canine kidney cells also have been shown to support viral replication in vitro. In addition, PCR protocols are available for sensitive and rapid detection of viral nucleic acid.[16]

As with most viral infection, there is no effective treatment for CnMV infections due to the rapid progression of disease. Vaccines are not available since the full impact of CnMV on canine health is unknown.[15]

Bluetongue Virus

Bluetongue is a noncontagious viral disease of domestic and certain wild ruminants caused by bluetongue virus (BTV), a member of the genus *Orbivirus* within family Reoviridae. Clinical evidence of BTV infection has been reported in sheep, some wild ruminants and, rarely, cattle. Multiple BTV serotypes and strains can colonize the pregnant uterus and, subsequently, the embryo and fetus. Reproductive failures occur in

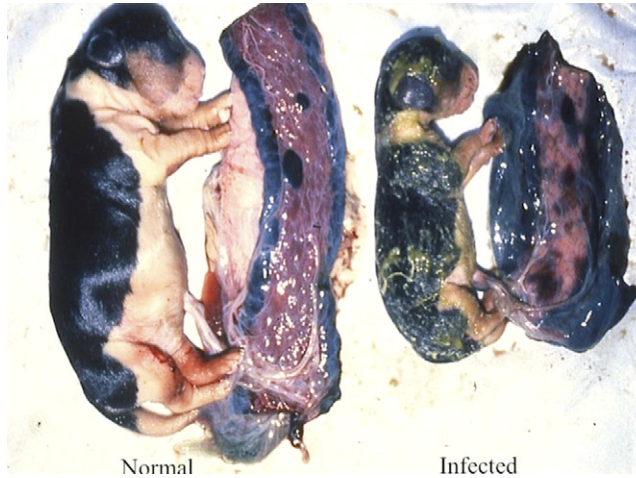

Fig. 5. Canine fetus (*right*) with experimental CnMV infection (late gestation). There is arrested fetal development in comparison to an uninfected puppy (*left*).

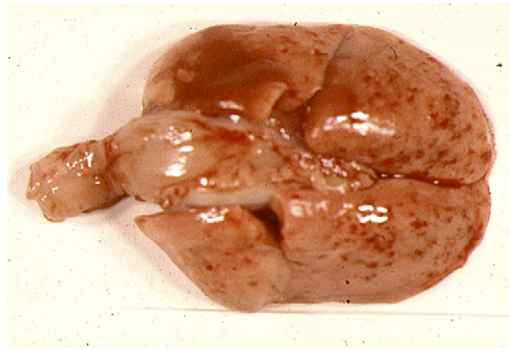

Fig. 6. Lung from a puppy with experimental CnMV neonatal infection. There are scattered areas of hemorrhage.

both pregnant sheep and cattle and include early embryonic death, abortion, and fetal malformations. Bulls and rams may be affected by temporary sterility or infertility.[25]

Bluetongue was reported in dogs in the United States that were given a multivalent canine vaccine contaminated by a BTV-11 strain.[26,27] The source appeared to be contaminated fetal calf serum that was used for cell propagation. This virus was responsible for abortion and/or death in late-term pregnant bitches, whereas non-pregnant dogs had only subclinical infections and seroconversion. The affected pregnant bitches presented with depression and fever within 2 to 3 days after vaccination and abortion few days later. Some of them developed severe respiratory distress and either died or were euthanatized. At necropsy, the animals appeared normal or displayed moderate gross lesions, mainly moderate to severe pulmonary edema. Postmortem findings similar to those commonly observed in BTV-infected sheep were present only in one case and included sanguineous pleural effusion, serous pericardial fluid, hemorrhagic areas in the lungs, and degenerated kidneys. Histopathology revealed pulmonary edema and congestion and placental vasculitis in all cases, with degenerative cardiomyopathy, diffuse glomerulonephropathy, and centrolobular hepatocellular degeneration being reported only in one bitch. These findings were confirmed by experimental inoculation of pregnant bitches with the contaminated vaccine or the isolated BTV-11 strain.[28,29]

For prevention of BTV infection in dogs, fetal calf serum and all bovine-derived products to be used in dogs should be screened for the presence of BTV.[25,26] Nothing is currently known about the transmission of BTV from infected dogs to susceptible ruminants. However, the occurrence of viremia in dogs that were administered contaminated vaccines[26,27] or those experimentally inoculated,[28,29] as well as the circulation of several BTV serotypes in African wild carnivores,[30] poses concerns about the potential epidemiologic role of domestic dogs in the context of BTV outbreaks involving ruminants.

FELINE VIRAL REPRODUCTIVE PATHOGENS

Feline Panleukopenia Virus

FPLV belongs to the feline parvovirus group of the Parvoviridae family (genus *Parvovirus*), together with canine parvovirus type 2 (CPV-2) and other parvoviruses of carnivores. FPLV-induced disease in cats has been known since the beginning of the 20th century, whereas CPV-2 emerged as pathogens of dogs only in the late 1970s.[31]

FPLV has maintained genetic stability,[32] whereas CPV-2 has experienced higher rates of nucleotide changes.[33,34] Within a few years after its first emergence, the "original" CPV-2 (1978 isolates) was completely replaced by 2 antigenic variants: CPV-2a and CPV-2b. A third antigenic variant (CPV-2c) was detected in Italy in 2000.[35] The latter variant is now spreading efficiently in the canine population worldwide.[31] CPV antigenic variants differ from the original type 2 by amino acid changes affecting the capsid protein and by their extended host range, which includes canine and feline cells in vitro and dogs and cats in vivo.[36] In fact, CPV-2a, CPV-2b, and CPV-2c viruses have been isolated from cats with clinical signs of feline panleukopenia.[37–41] Although CPV-2 has been tentatively associated with congenital cerebellar hypoplasia in pups, it is not recognized as a primary cause of reproductive failures in dogs. However, due to the expanded host range to cats, this virus might cause congenital infection in the feline species.

FPLV is shed in high amounts in the feces of infected cats. The virus, transmitted by the fecal-oral route, replicates in lymphoid tissues associated with the oropharynx, spreading to mitotically active tissues by both a cell-free and leukocyte-associated viremia. Target tissues include lymphoid organs, bone marrow, intestinal crypts, and, in pregnant queens, fetuses.[2,42] The clinical course and outcome of FPLV infection depend on the time when this is acquired (prenatal or postnatal). Postnatal infections of 2- to 6-month-old kittens result in the classic form of feline panleukopenia, characterized by fever, loss of appetite, depression, haemorrhagic diarrhoea, vomiting, and dehydration. A profound leukopenia involving all white blood cell (WBC) populations is constantly observed, with WBC counts ranging from 50 to 3000 cells/μL.[2] Intrauterine infections can cause different reproductive disorders that vary according to the stage of pregnancy at the moment of infection. Early in utero infections commonly result in infertility, early fetal death, and resorption, whereas in mid-gestation abortion or fetal mummification is more frequent. Queens that suffer abortion may not develop other clinical signs.

In the late stage of pregnancy, FPLV invades fetal nervous tissues, including the cerebrum, cerebellum, optic nerve, and retina. Virus-induced lesions are represented by hydrocephalus, hydranencephaly, cerebellar hypoplasia, optic nerve atrophy, and retinopathy. The cerebellum is the most damaged tissue, because, in cats, this part of central nervous system develops during late gestation and early neonatal periods.[43,44] The same lesions also may be observed when infection occurs within 10 days after birth. Cerebellar hypoplasia in FPLV-infected neonatal kittens is a consequence of Purkinje cell degeneration and interference with cortical development.[45,46] Newborn kittens with neurologic disorders due to FPLV perinatal infection often display tremors and incoordination due to the cerebellar injury and other neurologic disorders (seizures, behavioral changes) as a result of the forebrain damage. Retinal degeneration and optic nerve atrophy may lead to a certain degree of blindness. Gross pathologic changes in postnatal infections consist of hemorrhagic enteritis and lymphoadenopathy, which are characterized at the microscopic level by necrosis of the crypts and shortening of the villi in the intestine and by lymphocyte depletion in all lymphoid tissues. In utero infected kittens may have a spectrum of neurologic lesions (cerebellar hypoplasia, hydranencephaly, hydrocephalus) and thymic atrophy. Histologically, the most prominent change is the disruption of normal cerebellar architecture, with marked reduction of the granular and Purkinje cell layers. Vacuolation of the parenchyma, astrocytosis, and disruption of ependymal cells are also observed in the cerebrum of prenatally infected kittens.

A rapid diagnosis of FPLV infection is especially important in multicat households in order to isolate infected cats and prevent secondary infections of susceptible

contact animals. The clinical diagnosis of feline panleukopenia is inconclusive and it should be always confirmed by laboratory tests. Several methods have been developed for the laboratory diagnosis, which can be carried out on the faces or intestinal contents and on nervous tissues in postnatal and prenatal infections, respectively. Parvovirus infection in cats is diagnosed by means of immunochromatographic tests, virus isolation on feline cells, hemagglutination (HA), and PCR, but none of these methods is able to differentiate FPLV from CPV. Virus isolation on cell lines of different origin, hemagglutination inhibition (HI) tests with monoclonal antibodies (MAbs), or sequence analysis of large fragments of the main capsid protein VP2 gene can discriminate between the feline and canine parvoviruses, but they are not always applicable. Minor groove binder (MGB) probe assays have been used successfully for prediction of the CPV type in the dog feces,[47,48] as well as for discrimination between vaccinal and field strains of CPV,[49,50] even when these viruses are present simultaneously in the same samples.[51] An MGB assay also has been established for detection of FPLV and its rapid discrimination from CPV-2.[52]

Supportive therapy and nursing care reduce FPLV-associated mortality. In postnatal infections, parental fluid therapy is recommended to restore fluid, electrolytic, and acid-base balance. Restriction of oral intake of water and food is needed if vomiting persists and parenteral administration of broad-spectrum antibiotics may help prevent bacterial secondary infections. Antiviral therapy using feline recombinant interferon-omega has had variable efficacy in dogs with CPV-induced enteritis, but there are no data regarding the feline host.[42] There is no adequate treatment for neonatal kittens with FPLV-induced neurologic disorders.

Strict isolation is indicated when a cat is diagnosed with FPLV infection. The most effective prophylactic measure against FPLV infection is vaccination of susceptible cats. Both killed and modified-live virus (MLV) vaccines are available, but the latter are most effective and have been shown to provide protection for at least 6 years. The primary causes of FPLV vaccination failures are interfering levels of MDA that are transmitted by queens to their offspring through colostrum. Thus, in order to avoid interference with active immunization, vaccines should be administered to kittens only after MDA have waned.[42] In addition, MLV FPLV vaccines should never be administered to kittens less than 4 weeks of age to avoid cerebellar damage or to pregnant queens. Although some killed vaccines are licensed for use in pregnant queens, the value of vaccination is questionable and should be avoided.

There are concerns about the efficacy of FPLV-based vaccines against the CPV-2 antigenic variants. In a recent study,[53] an FPV-based vaccine protected against subsequent infection with a virulent CPV-2b strain. In that study, however, only 2 vaccinated cats were used, and they were challenged shortly after the administration of the second vaccine dose. Additional studies are required to confirm those findings, but the development of multivalent vaccines containing FPV in combination with a CPV variant strain might be considered.[40,41]

Feline Immunodeficiency Virus

Feline immunodeficiency virus (FIV) is a retrovirus of the genus *Lentivirus* that shares pathobiological features with human immunodeficiency virus (HIV). Although first identified only in 1986, FIV is now recognized as an endemic pathogen in the domestic cat populations worldwide, reaching a prevalence of 28% in some countries.[54] To date, at least 5 genetically distinct subtypes or clades have been defined according to the sequence diversity of the *env* gene, with clades A and B including most strains detected in the field.[55]

FIV transmission from infected to healthy cats occurs mainly by parental inoculation of free virus or virus-infected leukocytes through bite wounds, accounting for the higher prevalence in free-ranging intact male cats. Virus transmission from infected queens to their kittens is sporadically observed under natural conditions, but it is constantly reproduced in experimental infections. Vertical transmission also may occur in utero via the transplacental route, during parturition through direct contact with the genital secretions, or postpartum through ingestion of infected colostrum or milk. Milk has been shown to contain high concentrations of virus, which also occurs in mammary gland tissue. Not all kittens of the same litter become FIV infected. However, the high FIV-induced mortality, or progressive disease, in kittens born to FIV-positive queens observed under experimental infections suggests a higher frequency of natural in utero and neonatal infections than previously believed. Vertical transmission is more efficient when pregnant queens are infected during gestation. An increased rate of FIV infection with the advancement of pregnancy has been demonstrated. It was found that fetuses from cats infected with FIV at 3 weeks of gestation did not become infected, but up to 60% were found to be virus positive when queens were infected later in pregnancy.[56]

Transmission of virus between cats in stable households is uncommon.[57] Infected cats may remain healthy for several years before they develop disease signs and some cats never develop disease. The clinical course of FIV infection classically follows 3 stages: an acute phase of infection characterized by mild clinical signs (lethargy, fever, anorexia, lymphoadenopathy), a long-term asymptomatic phase, and a final phase, known as "acquired immunodeficiency syndrome–related complex." Typical signs of this phase are chronic gingivostomatitis, rhinitis and enteritis, lymphoadenopathy, weight loss, immune-mediated glomerulonephritis, neurologic disorders, and neoplasms. Also, secondary infections by opportunistic pathogens may occur.[57,58]

FIV infection may contribute to aberrant pregnancies and reproduction failures, resulting in arrested fetal development, abortion, stillbirth, and lowered birth weights.[59] A high rate of stillbirths or neonatal deaths has been observed in kittens born to FIV-infected queens, especially if infection had been acquired early in pregnancy.[56,60] Although data concerning fetal viability differ, an increased number of nonviable kittens, either due to arrested development or fetal resorption, has been reported in experimentally infected queens compared with uninfected queens.[61,62] The average birth weights and postnatal weight gains of FIV-infected kittens were generally lower than those of kittens born to uninfected queens, even in the absence of vertical transmission.[61] A different FIV distribution in fetal tissues has been detected according to the viral strain.[56,60]

Diagnostic tests for FIV are based on the detection of antibodies against the structural proteins (capsid protein p24 or transmembrane peptides) by in-house ELISA or immunochromatographic tests. Since young kittens born to FIV-infected queens may test falsely positive, due to the presence of MDA, they should be retested at 16 weeks of age. In addition, false-negative results may be related to the lack of seroconversion in the early stage of infection and to the immunodeficiency induced in the late stage of infection. In those cases, direct methods, such as PCR and real-time PCR, can be used to detect proviral DNA in circulating leukocytes. Due to the virus's variability, different PCR protocols provide variable sensitivity and some may not correctly detect all virus clades. Virus isolation is laborious and time-consuming, as it requires specialized expertise for co-cultivation of peripheral blood lymphocytes from suspected cats with primary feline T cells.[55]

Symptomatic cats should be administered supportive therapy to improve their general health. Administration of granulocyte (filgastrim), lymphocyte (insulin-like

growth factor-I), and erythrocyte (erythropoietin) stimulating factors may be beneficial. Antiviral drugs, mostly developed against HIV, are available for specific treatment of FIV infection, although some antiretroviral molecules have a higher toxicity in cats than in humans. These include AZT (3′-azido-2′,3′-dideoxythymidine) at the dosage of 5 to 10 mg/kg twice daily and AMD3100 at the dosage of 0.5 mg/kg twice daily. Feline interferon-omega, which has been recently licensed in several countries, has no side effects and can be administered lifelong, but its efficacy is still debated. In contrast, human interferon-alpha has been shown to significantly improve the survival rates of FIV-infected cats.[55] A killed vaccine is available in some countries, but its efficacy is uncertain. The only practical measure to control FIV transmission is the strict separation of infected cats and neutering of FIV-positive males, especially in multicat households, breeding catteries, and shelters. Cats should be tested before being introduced in new environments and, subsequently, on a yearly basis, which should help isolation of infected animals.[55]

Feline Leukemia Virus

Feline leukemia virus (FeLV) is a *Gammaretrovirus* of domestic and nondomestic felids that is classified into 4 subtypes (A, B, C, and T) on the basis of the host cell spectrum. FeLV-A is acquired from the field; FeLV-B arises from recombination between FeLV-A and endogenous retroviral sequences (enFeLV); FeLV-C originates from a mutation in the *env* gene; and FeLV-T is characterized by T lymphotropism. Another virus, feline sarcoma virus (FeSV), is the result of recombination between subtype A and cancer-associated cellular genes.[63] FeLV is shed in high amounts in the saliva, the main source of infection, and is easily transmitted through close contact between infected and susceptible cats. Consequently, animals living in multicat households, shelters, and breeding catteries are highly exposed to FeLV infection due to sharing of food and water dishes, mutual grooming, and sharing of common litter areas. Vertical transmission occurs frequently through the transplacental route or licking during nursing. Latently infected queens may also transmit the virus to their offspring due to FeLV reactivation during pregnancy.[64] Mammary colonization, in the absence of FeLV antigenemia, may represent an efficient source of vertical transmission via milk.[65] Kittens from infected queens may test antigen negative for several weeks or months, becoming positive only when the virus commences to replicate.[64]

In horizontal infections, virus replicates in lymphoid tissues of the oropharynx after entry. In some cats with efficient immune responses (early regressors), the virus is rapidly cleared from infected tissues, preventing systemic spread. When the immune response is not optimal, a FeLV viremia develops within lymphocytes and monocytes. In some cases, cats test positive by antigen-detection methods but only after weeks or months of infection. More commonly, however, there is a transient viremia (antigenemia is more preferable), but cats never recover from FeLV infection, remaining latently infected due to the presence of FeLV provirus in circulating mononuclear cells. Such animals often remain clinically healthy lifelong, unless immunosuppression or chronic stress causes virus reactivation. In cats with minimal immune responses, the virus causes a persistent viremia (antigenemia), reaching the bone marrow and other target tissues and inducing FeLV-related clinical signs. Due to the slow disease progression, signs may appear even after several years of viremia.[63]

FeLV disease includes a variety of clinical forms that are directly or indirectly caused by the virus replication in lymphoid tissues and bone marrow. Immunosuppression is the main consequence of FeLV infection and leads to exacerbation of the clinical course of infections caused by mild pathogens such as *Mycoplasma hemofelis* and other feline hemoplasmas, *Crytpococcus* spp, *Toxoplasma gondii*, feline

coronavirus, and calicivirus. In the late stages of infection, cats may develop different types of lymphomas and/or acute leukemias. A proportion of fibrosarcomas are associated with FeSV infection.[58,64]

Reproductive disorders can be observed in FeLV-infected queens. In utero infection can lead to fetal resorption, abortion, and neonatal death. Fetal resorption may be responsible for long periods of apparent infertility. Abortion occurs late in gestation with expulsion of normal-appearing fetuses and may be accompanied by bacterial endometritis. Kittens with perinatal infections may develop the "fading-kitten syndrome," which is characterized by an early fatal outcome due to failure to nurse, dehydration, hypothermia, and thymic atrophy.[64]

Due to the presence of "regressor cats," FeLV vaccination, and frequent production of antibodies against endogenous FeLV, serologic methods are not commonly used for FeLV diagnosis. Direct diagnosis is carried out by means of antigen- and nucleic acid–detection methods. ELISA and immunochromatographic tests detect a soluble protein (p27) in the blood or plasma that is produced in excess during active FeLV replication. Such tests are useful to diagnose the FeLV-associated clinical forms that are usually associated with virus replication in circulating mononuclear cells. However, the ELISA does not detect latent infections because of the lack of free p27 in the blood.[66,67] In addition, clinical forms induced by viral replication restricted to particular tissues (bone marrow, mammary glands, central nervous system) may be not diagnosed by antigen-detection methods. Gel-based and real-time PCR for proviral DNA detection are useful to identify cats with latent infection, although such animals may not develop FeLV-associated disease during their life. Reverse transcription (RT)-PCR and real-time RT-PCR detection of viral RNA produced by replicating virus in the saliva or other biological fluids may overcome these limitations, but, as antigen-detection methods, they cannot diagnose latent infections.[63]

Management of FeLV-diseased cats is difficult because of the variable clinical presentations. Supportive therapy consisting of fluid administration and blood transfusions should be considered in chronically infected animals. Corticosteroids should be avoided unless their administration is aimed to improve the food intake in the presence of chronic stomatitis. Antibiotics are required in the case of concurrent bacterial infections. As in the case of FIV, antiviral drugs may have severe side effects in cats. AZT and feline interferon-omega have been proved to improve the clinical and immunologic status, with increased quality of life and prolonged life expectancy in treated cats.[64,68,69]

Apart form the strict separation of infected cats, FeLV prophylaxis benefits from the availability of effective vaccines. Those vaccines have good efficacy in terms of protection from the clinical forms of disease, but none prevents FeLV infection.[70,71] In fact, several experiments have demonstrated that FeLV vaccination neither induces sterilizing immunity nor protects cats from infection.[71]

Felid Herpesvirus 1

Felid herpesvirus 1 (FeHV-1), a herpesvirus of the Alphaherpesvirinae subfamily, is responsible for a respiratory disease in domestic cats known as feline viral rhinotracheitis. The virus infects domestic cats and some wild felids and causes latent infections that are reactivated intermittently due to stress conditions, immunosuppression, or parturition, giving rise to viral shedding through oronasal and conjunctival secretions. Virus transmission occurs through direct contact with acutely infected cats and latently infected cats with virus reactivation, whereas indirect contact plays a role in shelters, breeding catteries, and multicat households. Newborn kittens

usually become infected through contact with oronasal secretions of the queens. In utero infections have been reported only under experimental conditions.[72,73]

Unlike with CaHV-1, FeHV-1–induced abortion is rarely observed and seems to occur more from debilitating effects than to direct virus involvement.[74] Although a brief period of viremia occurs during FeHV-1 primary infection,[75] there are no reports of isolation from the aborted fetuses in the field cases. FeHV-1 infection in a specific pathogen free cat colony involved 51 pregnant queens, but only 1 animal had a partial abortion. However, 61% of kittens born to infected queens developed FeVH-1–induced respiratory disease.[76] Intravenous inoculation of queens in late gestation resulted in abortion, stillbirth, or generalized neonatal infections, whereas there was no effect on gestation after intranasal inoculation.[76,77] Analogously, virus isolation from the genital tract of the queens and the tissues of their aborted fetuses was obtained only after intravenous FeHV-1 inoculation. This unnatural route of infection was the only one causing necrotic lesions in the uterus, placenta, and vagina of the queens and in the liver of the fetuses. Congenital infection of kittens also has been achieved by FeHV-1 instillation in the vagina of pregnant queens. In this experiment, kittens died in the first 3 weeks of life as a consequence of generalized infection. They had fibrinosuppurative rhinotracheitis, bronchopneumonia, and multifocal hepatic necrosis at the time of necropsy, with viral inclusions in the respiratory epithelium and hepatocytes.[78]

FeHV-1 infection is commonly diagnosed by virus isolation, using oropharyngeal and conjunctival swab samples inoculated into feline cell lines, or by PCR-based methods. Conjunctival smears also may be examined by immunofluorescence. Treatment of feline viral rhinotracheitis is mainly supportive and may require antibiotic administration for concurrent bacterial infections.[72] Antiherpetic drugs (trifluridine, idoxuridine, ganciclovir, feline interferon-omega) are used only for the treatment of FeHV-1 ocular disease. FeHV-1 prophylaxis is based on vaccination using both MLV and inactivated formulations. Analogous to other herpesvirus vaccines, FeHV-1 vaccines protect against the clinical disease but not infection and shedding of virulent virus.[73]

SUMMARY

Several viruses have been associated with reproductive failures in dogs and cats. Parvoviruses (CMV and FPLV) and herpesviruses (CaHV and FeHV) can cause pregnancy losses and neonatal mortality in both domestic dogs and cats, often with different pathogenetic mechanisms according to the carnivore species. Sporadic BTV infection has been reported in pregnant bitches vaccinated with contaminated products that resulted in abortion and stillbirth. In cats, retroviral infections caused by FIV and FeLV are commonly responsible for in utero virus transmission and pregnancy losses. Effective treatment protocols consisting of administration of antiviral drugs and prophylactic measures based on vaccination of susceptible animals are available only for few viral diseases; whereas therapy and prevention of other viruses impacting on canine and feline pregnancy are currently lacking.

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