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Canine Distemper Virus

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Canine distemper virus (CDV) belongs to the genus *Morbillivirus*, family Paramyxoviridae, along with phocid distemper virus, measles virus, rinderpest virus, peste-des-petits-ruminants virus, and cetacean Morbilliviruses [1].

CDV is the causative agent of a severe systemic disease in dogs characterized by a variety of symptoms, including fever, respiratory and enteric signs, and neurologic disorders. Clinical disease caused by CDV has been known for centuries and is described unequivocally in books of the seventeenth century, reporting large epidemics all over Europe [2].

The introduction of the modified-live (ML) CDV vaccines in the 1950s and their extensive use has greatly helped to keep the disease under control [3,4]. Notwithstanding, the incidence of CDV-related disease in canine populations throughout the world seems to have increased in the past decades, and several episodes of CDV disease in vaccinated animals have been reported [5,6].

CAUSE

CDV has an enveloped virion containing a nonsegmented negative-stranded RNA genome that encodes for a single-envelope–associated protein (M), two glycoproteins (the hemagglutinin H and the fusion protein F), two transcriptase-associated proteins (the phosphoprotein P and the large protein L), and the nucleocapsid protein (N) that encapsulates the viral RNA [1]. The H gene is a key protein for CDV itself and its animal hosts [3], because the virus uses this protein for attachment to receptors on the cell in the first step of infection. An adequate host immune response against the H protein may prevent CDV infection [7]. After attachment, the F protein promotes fusion of the cell membranes with the viral envelope. The F protein also promotes membrane fusion between the host cells, with formation of syncytia [8].

Field CDV strains do not replicate well in vitro, and virus adaptation to tissue cell cultures is fastidious. Canine or ferret macrophages may be used for adaptation of CDV to grow in vitro, whereas for propagation of cell-adapted CDV

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strains (used in the vaccines), canine kidney cell lines or Vero cells are used. Because the signaling lymphocyte activation molecule (SLAM) acts as a receptor for CDV, Vero cells expressing canine SLAM (VeroDog SLAM tag) have been engineered that allow efficient isolation of field CDV strains [9]. CDV replication in cells usually induces formation of giant cells (syncytia) with intracytoplasmatic and intranuclear eosinophilic inclusion bodies (Figs. 1 and 2).

EPIDEMIOLOGY

CDV has a broad host range, and evidence for the infection has been obtained in several mammalian species in the families Canidae, Mustelidae, Procyonidae, Ursidae, and Viverridae. The infection has also been described in captive and free-ranging large felids [10–12], in captive Japanese primates [13], in collared peccaries [14], and in Siberian seals [15].

Like other enveloped viruses, CDV is quickly inactivated in the environment and transmission mainly occurs by direct animal-to-animal contact or by exposure to infectious aerosol. The virus can be detected at high titers from secretions and excretions, including urine [16]. Routine disinfections and cleaning readily abolish virus infectivity.

Temporal fluctuations in disease prevalence have been observed, with increased frequency during the cold season. Age-related susceptibility to infection (3–6-month-old pups are more susceptible than older dogs) correlates with the decline in maternally derived immunity, because young pups are protected by passive immunity and most adult dogs are protected by vaccine immunization.

CDV is a monotypic virus, as defined by polyclonal antisera, although a variety of biotypes exist that differ in their pathogenic patterns [17]. Molecular techniques are useful to study virus epidemiology and to investigate the dynamics of circulation of the various strains in susceptible animals. Comparative studies of CDV strains have revealed that the H gene is subjected to higher genetic and antigenic variation than other CDV genes. The amino acid sequence

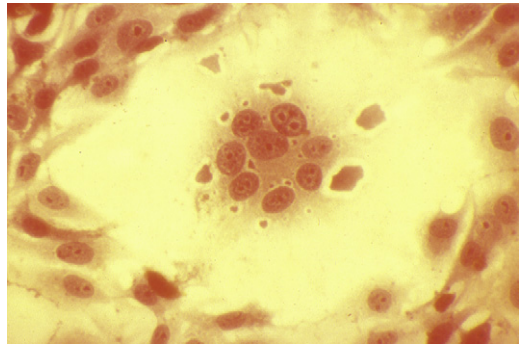

Fig. 1. Vero cells infected by CDV. There is formation of giant cells (syncytia) with intracytoplasmatic and intranuclear eosinophilic inclusion bodies.

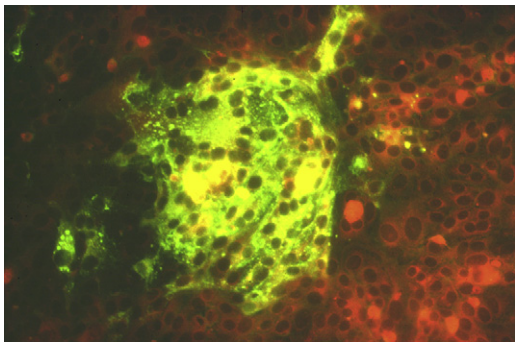

Fig. 2. Vero cells infected by CDV. The focus of viral replication is revealed by immunofluorescence.

of the F protein shows approximately 4% variability among different CDV strains, which is in the range of variability of the other structural proteins, whereas the CDV H proteins vary by approximately 10%. Sequence variation in the H protein may affect neutralization-related sites with disruption of important epitopes. Based on the pronounced genetic diversity in the H gene, it is possible to characterize most CDV field strains into six major genetic lineages, referred to as America-1 and -2, Asia-1 and -2, European, and Arctic [18–22], that are variously distributed according to geographic patterns but irrespective of the species of origin. The greatest genetic and antigenic diversity is between the vaccine strains (America-1 lineage) and the other CDV lineages [5,23–27]. Sera raised against field CDV isolates may have neutralizing titers up to 10-fold higher against the homologous virus than against vaccine strains [10]. Although it is unlikely that such antigenic variations may affect the protection induced by vaccine immunization, it is possible that critical amino acid substitutions in key epitopes of the H protein may allow escape from the limited antibody repertoire of maternal origin of young unvaccinated pups, increasing the risk for infection by field CDV strains. Some CDV strains seem to be more virulent or are associated with different tropism, but this relies on individual variations among the various strains rather than on peculiar properties inherent to a given CDV lineage [17,28].

CLINICAL SIGNS AND PATHOLOGIC FINDINGS

The virus enters the new host by the nasal or oral route and promptly starts replication in the lymphoid tissues [29], resulting in severe immunosuppression. T cells are more affected than B cells [30]. The decrease in CD4+ lymphocytes is quick and persists for several weeks. Because the percentage of CDV-infected lymphocytes is low, the mechanisms of immunosuppression are not clear. Immunosuppressive activity has been displayed by the N protein of measles virus, and the same mechanisms likely trigger immunosuppression in CDV infection [31,32].

The incubation period may range from 1 to 4 weeks or more. Transient fever reaches a peak 3 to 6 days after infection and is associated with the initial virus spread in the body. Loss of appetite, slight depression, ocular and nasal discharge, and tonsillitis may be observed (Fig. 3). By days 6 to 9 after infection, CDV spreads by cell-associated viremia to the epithelial cells in most organs [33,34].

At this stage, the outcome of the infection and the severity of the signs vary markedly on the basis of strain virulence, the age of the animal, and the immune status. If the dog develops a strong immune response, the virus gets cleared from the tissues and the animal completely recovers from the infection. When dogs develop a weak immune response, the virus is able to reach the epithelial tissues and the central nervous system (CNS). The initial clinical signs disappear, but the virus persists for extended periods in the uvea, neurons, or urothelium and in some skin areas (foot pads). The CNS signs are delayed, and hyperkeratosis is observed in some dogs. In the dogs that fail to mount an immune response, the virus continues to replicate and spreads massively throughout the body. Localization in the CNS results in acute demyelinization, and most dogs die 2 to 4 weeks after the infection [34,35].

As a result of the epithelial localization, respiratory, intestinal, and dermatologic signs occur by 10 days after infection. The symptoms are often exacerbated by secondary bacterial infections and include purulent nasal discharge, coughing, dyspnea, pneumonia, diarrhea, vomiting, and dermal pustules. Enamel hypoplasia and hyperkeratosis of the foot pads and nose are typical signs of CDV infection and may be observed in dogs that survive subclinical or subacute infections (Figs. 4 and 5) [36].

Starting from 20 days after infection, neurologic signs may be observed, such as circling, head tilt, nystagmus, partial or complete paralysis, convulsions, and

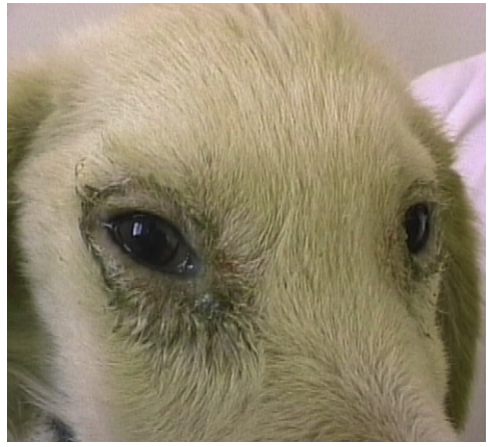

Fig. 3. Dog with CDV infection. There is conjunctivitis with periocular discharge.

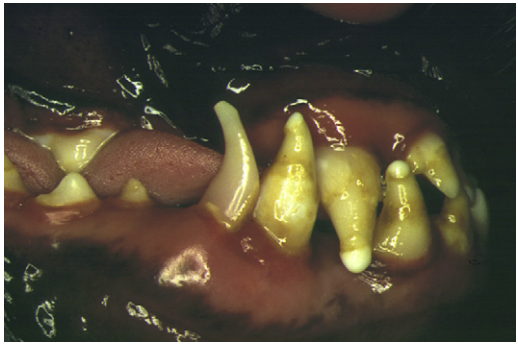

Fig. 4. Dog with CDV infection. There is marked enamel hypoplasia.

dementia. Involuntary jerky twitching or contraction of muscles and convulsions preceded by chewing-gum movements of the mouth are considered typical of CDV infection. Neurologic signs may also be observed at 40 to 50 days after infection as a consequence of chronic CDV-induced demyelination. The virus persists in the CNS, and the disease evolves discontinuously but progressively. Some dogs may still recover, but compulsive movements (eg, head pressing, continual pacing, uncoordinated hypermetria) tend to persist [36].

Intracytoplasmic eosinophilic inclusion bodies are present in the epithelial cells of the skin, bronchi, intestinal tract, urinary tract, bile duct, salivary glands, adrenal glands, CNS, lymph nodes, and spleen [36].

Demyelination is the prominent lesion in the brain of dogs that are infected with CDV. In acute infection, primary demyelination is not related to inflammation [37], because perivascular cuffs are not visible, and it is likely accounted for by metabolic dysfunction with decreased myelin synthesis in CDV-infected oligodendrocytes and by virus-induced activation of microglial cells [38].

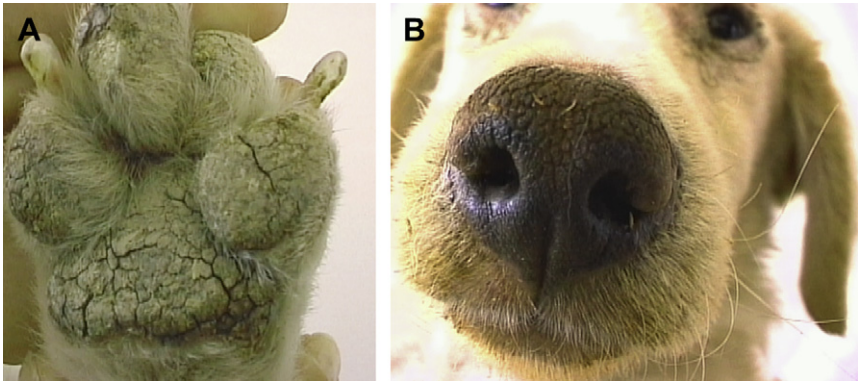

Fig. 5. Dog with CDV infection. There is hyperkeratosis of the foot pads (*A*) and nose (*B*).

In chronic forms of disease, the demyelination lesions are attributable to an inflammatory reaction elicited by a CDV-specific immune response and by persistence of CDV infection in the tissues. Experiments in vitro suggest that chronic inflammatory demyelination is attributable to an "innocent bystander mechanism" resulting from interactions between macrophages and virus-antibody complexes [39]. Perivascular cuffing with lymphocytes, plasma cells, and monocytes is present in the areas of demyelination.

A rare outcome of CDV infection is chronic encephalomyelitis of mature dogs, termed *old dog encephalitis* (ODE) [40]. ODE presents as a progressive cortical derangement with a wide range of clinical signs and usually occurs in dogs with a complete vaccination history. Frequent lesions associated with ODE are multifocal perivascular and parenchymal lymphoplasmacytic encephalitis in the cerebral hemispheres. The disease seems to develop in dogs after acute CDV infection when the virus gains the capability to persist in the nervous tissues. An ODE-like disease has been reproduced experimentally in a gnotobiotic dog infected with a neurovirulent CDV strain [41]. The molecular mechanisms triggering persistence of CDV in the CNS are not clear. Changes in proteins H, F, and M, or in their interactions, may affect CDV fusogenicity in vitro and are likely involved in the genesis of ODE [42,43].

DIAGNOSIS

CDV should be considered in the diagnosis of any febrile condition of puppies with multisystemic symptoms. Several laboratory tests are available to confirm CDV infection. Immunofluorescence (IF) on conjunctival, nasal, and vaginal smears (Fig. 6) is not sensitive and can detect CDV antigens only within 3 weeks after infection, when the virus is still present in the epithelial cells [3]. Virus isolation on cell lines from clinical or autoptic samples (eg, conjunctival swabs, buffy coat, spleen and lung tissues) is fastidious. Molecular assays, such as reverse transcriptase polymerase chain reaction (RT-PCR) [44–47] and real-time RT-PCR [16], are sensitive and specific. A nested RT-PCR system

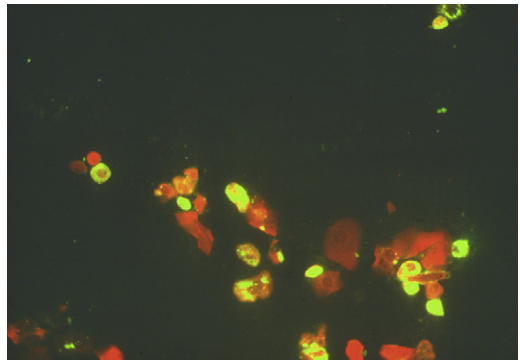

Fig. 6. IF examination for CDV on a conjunctival smear from a dog.

with specific probes allows characterization of the various CDV lineages and distinction between field and vaccine CDV strains [48].

High antibody titers to CDV may be detected for several months after vaccination or after subclinical or clinical infection by ELISA, virus neutralization, or indirect IF assays. Virus-specific immunoglobulin M (IgM) persists for at least 3 months after infection and may be specifically recognized by ELISA [49,50] and used as a marker of recent CDV infection.

TREATMENT AND PREVENTION

Treatment consists of supportive care and antibiotics and is aimed at preventing the secondary bacterial infections that are frequent in immunosuppressed animals. Ribavirin, a purine nucleoside analogue, is capable of inhibiting CDV replication in vitro [51], but antiviral drugs are not available commercially.

ML vaccines are recommended for immunization of dogs. The vaccines elicit long-lasting protective immunity. Several vaccine strains (eg, Onderstepoort, Rockborn, Snyder Hill) have been used [3]. Some CDV vaccine strains may retain pathogenicity when used in wild-life animals [52] or when administered in conjunction with canine adenovirus-type 1 [53,54]. Also, immune depression induced by stress or by concomitant diseases may result in reversion to virulence of the vaccine [55,56]. Although vaccine-induced disease is always suspected in dogs that develop distemper shortly after immunization, in most cases, the disease is induced by wild-type CDV infecting pups before active immunization is elicited. Vaccine failures are mostly attributable to incorrect vaccinal protocols or to vaccine alteration after improper storage.

A recombinant viral vaccine for CDV has also been produced [57]. The vaccine proved to be effective and safe, because the virus vector does not replicate efficiently in mammals.

A major problem encountered in CDV vaccination of young pups is the lingering passive immunity of maternal origin that may prevent active immunization. Because measles virus is closely related to CDV, heterologous vaccination with the human Morbillivirus has been adopted to immunize pups in the face of maternally derived immunity. The vaccine seems to have limited efficacy [58] and introduces a human pathogen into the environment. The vaccine is not authorized in Europe, although it is available in the United States.

To overcome the interference of maternally derived antibodies, pups should be vaccinated with ML CDV vaccine at 6 to 8 weeks of age and again after 2 to 4 weeks. Annual revaccination is usually performed. Because protective immunity induced by ML vaccines persists for more than 3 years [59], vaccination of the animals is recommended every 3 years.

SUMMARY

Vaccine-based prophylaxis has greatly helped to keep distemper disease under control [3,4]. Notwithstanding, the incidence of CDV-related disease in canine populations throughout the world seems to have increased in the past decades,

and several episodes of CDV disease in vaccinated animals have been reported [5,6], with nation-wide proportions in some cases [60]. In parallel, in the past decades, uncontrolled trading of low-cost and high-value breed pets from countries with low sanitation standards has been intensifying in several European countries, leading to emergence or re-emergence of infectious threats to the health of dogs [61]. Recently, the spread of unusual CDV strains (termed *Arctic* after their similarity to CDV strains identified in animals of the Arctic ecosystem) has been documented in Europe, and similar CDV strains have been identified in North America [22,62,63]. The reasons for and effects of these changes in CDV epidemiology are unknown. Increasing surveillance should be pivotal to identify new CDV variants and to understand the dynamics of CDV epidemiology. In addition, it is important to evaluate whether the efficacy of the vaccine against these new strains may somehow be affected.

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