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CHAPTER 18

Infectious Canine Hepatitis

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Overview of Infectious Canine Hepatitis

First Described: First described as infectious canine hepatitis (ICH) in 1947 in Sweden by Rubarth[1]; CAV-1 was first isolated in chick embryos in 1951[2]

Cause: Canine adenovirus-1 (family Adenoviridae, genus *Mastadenovirus*)

Affected Hosts: Dogs, coyotes, foxes, wolves, bears, skunks

Geographic Distribution: Worldwide

Mode of Transmission: Direct contact with infected saliva, feces and urine, and contaminated fomites

Major Clinical Signs in Dogs: Fever, lethargy, inappetence, vomiting, hemorrhagic diarrhea, abdominal pain, dehydration, conjunctivitis, petechial hemorrhages, tachypnea, cough, corneal edema ("blue eye"), rarely icterus or neurologic signs.

Differential Diagnoses: Other systemic viral diseases such as parvoviral enteritis and canine distemper, enteric viral and bacterial infections, hepatotoxicosis (e.g., mushrooms), Rocky Mountain spotted fever, gastrointestinal foreign body, dietary indiscretion, leptospirosis, portosystemic shunting with hepatic encephalopathy, disseminated fungal infections (especially systemic candidiasis), systemic protozoal infections (especially sarcocystosis, toxoplasmosis or African trypanosomiasis), hemic neoplasia (especially lymphoma).

Human Health Significance: CAV-1 does not infect humans.

Etiology and Epidemiology

Infectious canine hepatitis (ICH) is an uncommonly recognized disease of dogs that is caused by canine adenovirus type 1 (CAV-1), a non-enveloped, icosahedral double-stranded DNA virus that is antigenically related to CAV-2 (see Chapter 17) (Figure 18-1). CAV-1 also causes disease in wolves, coyotes, skunks, and bears, as well as encephalitis in foxes, but the diversity of wildlife hosts is not as great as that for CDV. Ferrets are not susceptible.[3] ICH has also been referred to as Rubarth's disease, after Carl Sven Rubarth, a veterinarian who first described the disease in the late 1940s.[1] Over the subsequent 10 years, ICH was described worldwide, including the United States, Canada, United Kingdom, Australia, Japan, Brazil, and throughout Europe. The virus can survive for months at room temperature, but should be readily inactivated by disinfectants with activity against canine parvovirus (CPV).[4] Disease most commonly occurs in dogs that are less than 1 year of age, but was reported in adult dogs before widespread vaccination for ICH was introduced.

The strong antigenic relationship between CAV-1 and CAV-2 is clinically important, because vaccines that contain CAV-2 protect against infection with CAV-1 and vice versa. After the introduction of CAV-1 vaccines, ICH largely disappeared, but over the past decade it has reemerged, with published reports of disease from Italy, Switzerland, and the United States.[5-8] Disease in Europe has been associated with puppy trading from kennels in eastern European countries and possibly spillover of virus circulating in wildlife.[9] In Italy, three outbreaks occurred in shelters in southern Italy, and the others involved purebred puppies imported from Hungary a few days before the onset of clinical signs. Several of the dogs were co-infected with other viruses, such as canine distemper virus (CDV), CPV, or canine enteric coronavirus. Encephalopathy due to CAV-1 infection was described in nine 5-week-old Labrador retriever puppies from Arkansas in the United States, all of which belonged to the same litter.[8] The litter was from an unvaccinated bitch. These case descriptions confirm that CAV-1 continues to circulate in the dog population and can result in severe disease in young dogs when vaccination does not occur, is improperly timed, and stress, co-infections, and overcrowded conditions prevail.

Clinical Features

Signs and Their Pathogenesis

CAV-1 is shed in saliva, feces, and urine, and transmission occurs through direct dog-to-dog contact or contact with contaminated fomites such as hands, utensils, and clothing. Ectoparasites such as fleas and ticks are also potential mechanical vectors.[4] Airborne transmission does not appear to be important. Initial infection occurs through the nasopharyngeal, conjunctival, or oropharyngeal route, and the virus replicates within the tonsils, after which it spreads to regional lymph nodes and the bloodstream via lymphatics. Subsequently, infection of hepatocytes and endothelial cells within a variety of tissues occurs, such as the lungs, liver, kidneys, spleen, and eye with resultant hemorrhage, necrosis, and inflammation. The virus replicates in the nucleus of host cells, where crystalline arrays of virions form. There is severe condensation and margination of nuclear chromatin, with inclusion body formation (Figure 18-2). The virions are released by cell lysis, which leads to tissue injury and disseminated intravascular coagulation (DIC). Within the liver, the virus initially infects Kupffer's cells and subsequently spreads to hepatocytes.

Clinical signs generally occur after an incubation period of 4 to 9 days, although many dogs probably show no signs of illness.[4] Three overlapping disease syndromes have been described. The first is peracute disease with circulatory collapse, coma, and death after a brief illness that lasts less than 24 to 48 hours. The second, most commonly described syndrome is acute disease, which is associated with high morbidity and reported mortality rates of around 10% to 30%.[4] Dogs with acute disease

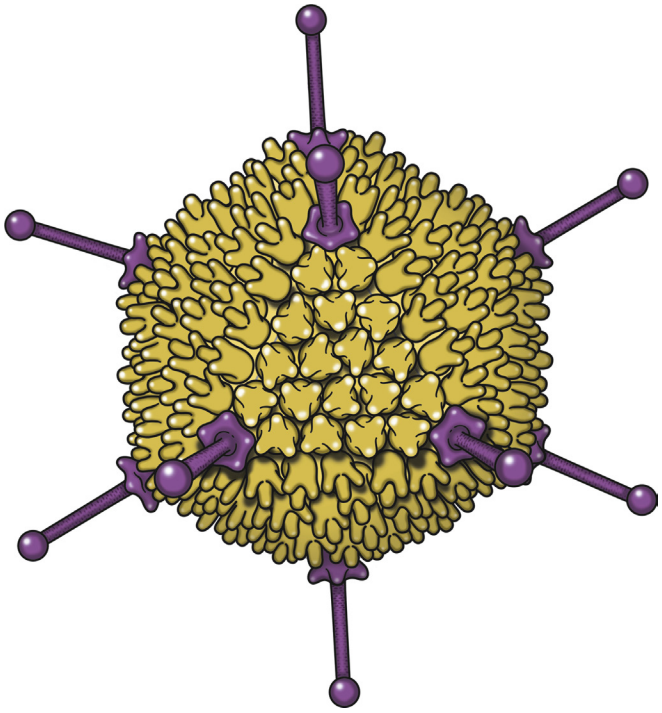

FIGURE 18-1 Structure of canine adenovirus. The virus is a non-enveloped, Icosahedral virus with fibers (purple) that radiate outwards from the virion.

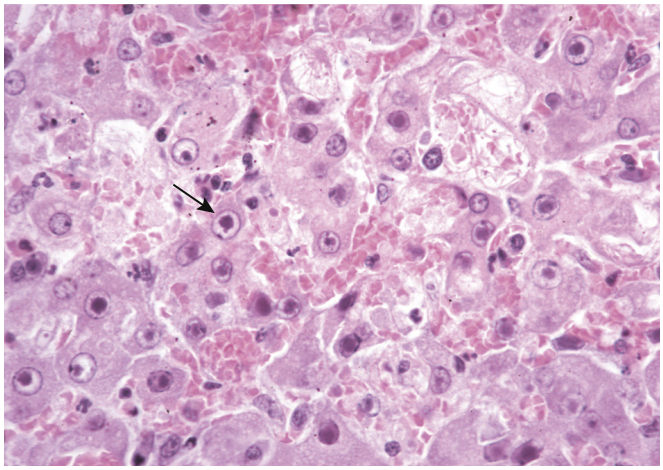

FIGURE 18-2 Infection of hepatocytes and endothelial cells with CAV-1 produces characteristic basophilic intranuclear inclusions surrounded by a clear zone that separates them from the marginated chromatin *(arrow)*. H&E stain. (Courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia and Noah's Archive, College of Veterinary Medicine, The University of Georgia. In Zachary JF, McGavin M. Pathologic Basis of Veterinary Disease, 5 ed. St. Louis, MO: Mosby; 2012.)

either recover or die within a 2-week period. The third is a more chronic form that occurs in dogs with partial immunity, with death due to hepatic failure weeks (subacute disease) or months (chronic infection) after initial infection.[10]

Acute disease is variably characterized by the presence of fever, tonsillitis, conjunctivitis, inappetence, lethargy, weakness, polydipsia, vomiting, hematemesis, diarrhea, cough, tachypnea, and icterus. Diarrhea may contain frank blood or melena. Widespread petechial and ecchymotic hemorrhages and hematuria can be seen. Corneal edema ("blue eye") occurs in the first week of illness and results from replication of virus within corneal endothelial cells (Figure 18-3). Rarely, neurologic signs such

FIGURE 18-3 Young adult dog with corneal edema from an Italian shelter outbreak of CAV-1 infection. (Courtesy Dr. Nicola Decaro, Department of Veterinary Public Health, Faculty of Veterinary Medicine of Bari, Italy.)

as seizures, ataxia, circling, apparent blindness, head pressing, and nystagmus have been reported in association with CAV-1 encephalitis.[7,8] The development of neurologic signs may also represent hepatic encephalopathy, intracranial thrombosis or hemorrhage, or, as occurred in one outbreak, concurrent infection with CDV.[7]

The antibody response appears 7 days after infection and limits tissue damage. Viral persistence within the renal glomeruli, uveal structures of the eye (the iris and ciliary body), and the cornea can trigger immune complex formation in dogs that recover from acute illness. This leads to glomerulonephritis with proteinuria, severe uveitis, and persistent corneal edema in some surviving dogs. Glomerulonephritis usually occurs about 1 to 2 weeks after the acute signs resolve. Glomerular lesions contain deposits of viral antigen, IgG, IgM, and C3.[11,12] Infection of the glomerular endothelium is followed by a persistent tubular infection, development of interstitial nephritis, and viruria, but chronic renal failure has not been described. Viral shedding in the urine can occur for up to 6 to 9 months after infection. Anterior uveitis is associated with massive influx of inflammatory cells into the anterior chamber. Occasionally persistent corneal edema fails to resolve for months and may be associated with complications such as glaucoma.[13] The Afghan hound is reportedly susceptible to this complication.[14]

In experimental infections with CAV-1, chronic hepatitis with extensive fibrosis was observed in some dogs that recovered from acute illness, with survival for up to 8 months.[10] The virus could not be found in hepatic lesions from these dogs. Attempts to detect CAV-1 in the liver of other dogs with chronic active hepatitis using PCR assays have to date been unrewarding.[15-17]

Physical Examination Findings

Physical examination findings in dogs with acute ICH vary, but might include lethargy, dehydration, fever (up to 106°F or 41°C),

TABLE 18-1

Diagnostic Assays Available for Infectious Canine Hepatitis

Assay	Specimen Type	Target	Performance
Histopathology	Usually necropsy specimens, but also liver biopsy	Hepatic necrosis with intranuclear inclusions; CAV-1 antigen with immunohistochemistry	True sensitivity and specificity of inclusion visualization unknown. Liver biopsy may not be feasible because of coagulopathies.
Polymerase chain reaction (PCR)	Blood; rectal, conjunctival and nasal swabs; urine; tissues collected at necropsy	CAV-1 DNA	Sensitivity and specificity may vary depending on assay design. Specific CAV-1 assays are not widely offered by commercial veterinary diagnostic laboratories. Some assays differentiate between vaccine (CAV-2) and field virus (CAV-1). The significance of a positive result from urine may be difficult to interpret due to subclinical shedding. False-negative results may occur as a result of PCR assay inhibition by components of feces or in dogs with subacute or chronic presentations.
Virus isolation	All body secretions, tissues	CAV-1	Sensitive and specific, but generally only available as a research tool.

CAV, Canine adenovirus.

congestion and enlargement of the tonsils (which may be severe), pallor, conjunctivitis, peripheral lymphadenopathy, tachypnea, increased lung sounds, and tachycardia. In some reports, serous to mucopurulent ocular and nasal discharge have been observed, but these may have resulted from co-infections with other respiratory viruses.[4] Abdominal palpation may reveal hepatomegaly, splenomegaly, or abdominal pain. Icterus is uncommon but can occur in dogs with a more prolonged course of disease. Peripheral edema that involves the head, neck, and ventral abdomen has been described.[18] Puppies with CAV-1 encephalitis may show signs of circling, vocalization, head pressing, ataxia, and blindness.[8] Coagulopathies may be manifested as cutaneous or mucosal petechial hemorrhages; gingival hemorrhages; epistaxis; or prolonged bleeding from venipuncture sites.

Ocular complications occur in at least 20% of affected dogs. Unilateral or, less commonly, bilateral corneal edema may be observed, which initially develops at the limbus and is occasionally associated with blepharospasm, photophobia, and a serous ocular discharge.[13] Unilateral involvement may progress to bilateral involvement over several days. Using a slit lamp, the cornea is markedly thickened, and there is episcleral and ciliary injection. Uveitis may also be apparent. Corneal ulceration and increased intraocular pressure has also been described in dogs with corneal edema, the latter of which may result in blindness.[13]

Diagnosis

ICH should be suspected in any dog less than 1 year of age that has a questionable vaccination history and signs of fever, respiratory, gastrointestinal, and hepatic disease, and certainly in any young dog that develops corneal edema. Diagnosis is easily achieved at necropsy when characteristic intranuclear inclusion bodies are seen in tissues, but the sensitivity and specificity of this finding is unknown. Inclusion bodies may be seen on impression smears of liver biopsies or tissue obtained at necropsy. At the time of writing, antemortem diagnosis is challenging owing to the lack of commercially available assays that specifically detect the virus or viral DNA, and the disease may be underdiagnosed (Table 18-1). Serologic assays are available, but they provide only retrospective diagnosis, and interpretation of these assays may be a challenge when there is a history of vaccination.

Laboratory Abnormalities

Complete Blood Count

Findings reported on the CBC are variable and include leukopenia, anemia, increased nucleated red blood cells, and moderate to severe thrombocytopenia. Leukopenia occurs early in the course of infection and may be profound. Initially there is a lymphopenia, after which neutropenia occurs and worsens progressively until death.[18] Increased band neutrophils and toxic changes may also be present. Occasionally leukocytosis is observed.[19] Leukocytosis and lymphocytosis may occur as part of the recovery process.

Serum Biochemical Tests

Changes on the serum biochemistry profile include increased activity of serum ALT (sometimes >1000 U/L) and ALP, hyperbilirubinemia, hypoglycemia, and hypoalbuminemia.[20] Determination of serum ammonia concentration may facilitate diagnosis of hepatic encephalopathy in dogs with neurologic signs.

Urinalysis

The urinalysis of dogs with ICH may reveal proteinuria, hyaline and granular cylindruria, hematuria, and bilirubinuria.

Coagulation Profile

In addition to thrombocytopenia, coagulation abnormalities reported in ICH reflect the presence of DIC and hepatic failure and include prolonged prothrombin time, markedly prolonged activated partial thromboplastin time (to 6 to 7 times control values), decreased factor VIII activity, hypofibrinogenemia, and increased fibrinogen degradation products. Platelet function assays have shown reduced platelet adhesion.[18]

Diagnostic Imaging

Findings on plain radiography and abdominal sonography in dogs with ICH have not been reported. Plain radiography might reveal a normal to slightly enlarged liver, and poor detail as a

result of abdominal effusion or the young age (and therefore low intra-abdominal fat content) of affected dogs.

Microbiologic Tests

Virus Isolation

CAV-1 can be readily isolated in a variety of cell types, such as Madin-Darby canine kidney cells.[7,8] In dogs with acute illness, any body fluid or tissue is likely to contain sufficient virus for isolation. Cultures are evaluated for a cytopathic effect with intranuclear inclusions, and the presence of CAV-1 is confirmed using immunostaining. Isolation is not widely offered by commercial veterinary diagnostic laboratories.

Serologic Diagnosis

Serologic tests are available commercially for detection of IgG and IgM against CAV-1, which include ELISA assays, hemagglutination-inhibition, and serum neutralization. Unfortunately, dogs with acute disease may die before they develop antibodies to the virus.[10] For dogs that recover from illness, a recent history of vaccination may complicate interpretation of acute and convalescent phase serology. In the absence of a vaccination history, a fourfold rise in titer over a 2- to 3-week period together with compatible clinical signs is supportive of the diagnosis of ICH. Titers that follow natural infection may be higher than those that follow vaccination.

Molecular Diagnosis Using the Polymerase Chain Reaction

Conventional PCR assays for detection of CAV-1 in clinical specimens such as nasal, rectal, and ocular swabs and blood, as well as tissue obtained at necropsy, have been described. These include assays that differentiate between CAV-1 and CAV-2[21] and represent one of the most rapid means of antemortem diagnosis. Because of the rarity of the disease, the clinical sensitivity and specificity of these assays are not well understood. Real-time PCR assays that specifically detect CAV-1 infection were not available at the time of writing (see Chapter 5 for a discussion of the differences between conventional and real-time PCR assays). The results of PCR assays on urine may be more difficult to interpret than those for other specimens, because of the potential for chronic shedding from this site in the absence of clinical signs. Assays that specifically detect CAV-1 differentiate between virulent CAV-1 virus and vaccine virus, because vaccines for ICH all contain only CAV-2.

Pathologic Findings

Gross Pathologic Findings

Gross pathologic findings in dogs with ICH include blood-tinged ascites or hemoabdomen; a slightly enlarged, congested or mottled liver; mild splenomegaly; enlarged, congested, and edematous lymph nodes; and fibrin deposition on the surface of abdominal viscera (Figure 18-4). The gallbladder wall is typically markedly thickened and edematous. Petechial and ecchymotic subserosal hemorrhages may be apparent in multiple viscera, and the intestinal tract may contain bloody fluid. The brain may also contain petechial hemorrhages or areas of gray discoloration.[8] Parenchymal organs may contain fibrin thrombi. Occasionally, multifocal pulmonary consolidation and/or serosanguineous pleural fluid is noted.

Histopathologic Findings

Histopathologic findings are variable and depend on the course of infection and possibly the virus strain. The most characteristic finding is hepatocellular necrosis and intranuclear viral inclusion bodies within Kupffer's cells and hepatocytes, and a mixed

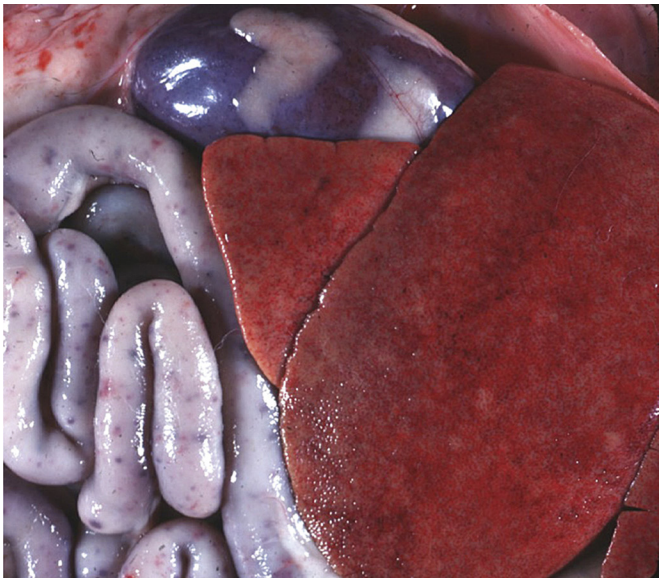

FIGURE 18-4 Infectious canine hepatitis, hepatic necrosis, liver, dog. The liver from dogs with ICH can be slightly enlarged and friable with a blotchy yellow discoloration. Sometimes fibrin is evident on the capsular surface. Note the petechiae on the serosal surface of the intestines caused by vascular damage. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. In Zachary JF, McGavin MD. Pathologic Basis of Veterinary Disease, 5 ed. St. Louis, MO: Mosby; 2012.)

inflammatory cell infiltrate (see Figure 18-2). Fibrosis may be observed in dogs with chronic liver injury. Interstitial nephritis, with focal accumulations of neutrophils, mononuclear cells, and fibrosis, may also be present,[22] as well as evidence of widespread hemorrhage, thrombosis, and necrosis as a result of DIC. Findings in dogs with CAV-1 encephalitis have included mild spongiosis, neuronal necrosis, hemorrhage, and perivascular cuffing with mononuclear cells.[8] Viral inclusion bodies may be found in endothelial cells of meningeal vessels, the cornea, renal glomeruli, and the tonsils. Immunohistochemistry can be used to confirm the presence of the virus within tissues.

Treatment and Prognosis

Supportive Care

Treatment of dogs with acute ICH is purely supportive and consists primarily of fluid therapy, including crystalloid fluids and blood products. Fluid therapy should be aggressive with careful monitoring and avoidance of overhydration, because of increased vascular permeability and hypoalbuminemia. Fluids should be supplemented with electrolytes and dextrose as required. Other medications that may be indicated include antiemetics, antacids, sucralfate, whole blood or plasma transfusions, and colloids such as hetastarch. Partial or total parenteral nutrition may be indicated for severely affected dogs that do not tolerate enteral feeding. Dogs with DIC may require treatment with heparin in addition to plasma. Management of hepatic encephalopathy with lactulose enemas, oral lactulose (in the absence of vomiting), and poorly absorbed oral antimicrobial drugs such as ampicillin may also be indicated. The use of parenteral broad-spectrum antimicrobial drugs should be considered for dogs with hemorrhagic gastroenteritis that may develop bacteremia as a result of bacterial translocation. After fluorescein staining has shown no evidence of corneal ulceration, dogs with severe corneal edema and uveitis should be treated with topical ophthalmic preparations that contain glucocorticoids and atropine to prevent development of glaucoma.

Prognosis depends on the severity of disease, which reflects the immune status of the affected dog and possibly the virus strain. There is a possibility that recovered dogs may develop chronic hepatitis or chronic glomerulonephritis, but the extent to which this truly occurs is unknown.

Immunity and Vaccination

Immunity to natural infection with CAV-1 is probably lifelong. Effective vaccines have been available and widely used as part of core vaccine programs for dogs for many years. Immunity after immunization with attenuated live vaccines lasts at least 3 years and probably longer. Early vaccines, which contained CAV-1, were associated with the development of corneal edema and glomerulonephritis in a small percentage (<1%) of immunized dogs. Replacement of attenuated live CAV-1 with CAV-2 occurred after 1980 and eliminated this complication.[23] These vaccines have the potential to cause transient respiratory signs and tonsillitis in dogs if accidental inhalation occurs, so care should be taken not to aerosolize the vaccine during administration. Maternal antibody persists until puppies are 12 weeks of age and interferes with immunization when virus neutralization titers exceed 1:100. Vaccines should be administered every 3 to 4 weeks from 6 weeks of age, with the last vaccine given no earlier than 16 weeks of age (see Appendix). Vaccine virus may be shed from the respiratory tract by dogs after vaccination, which has the potential to immunize other dogs as well. It has been suggested that this phenomenon may have been responsible for the virtual disappearance of the disease in the dog population in regions where vaccination is widely performed.[24]

Prevention

The best means of prevention of ICH is proper vaccination. Additional control measures that could be considered in locations where outbreaks occur, such as in shelters, include proper disinfection, isolation, and prevention of overcrowding and other co-infections, which may worsen disease. Because contact with wild animal species such as coyotes, wolves, and foxes that might be shedding the virus may also be a source of infection for dogs, exclusion of these species from interactions with domestic dogs may also serve to prevent the disease.

Public Health Aspects

There is no evidence that CAV-1 infects humans.

SUGGESTED READINGS

Decaro N, Campolo M, Elia G, et al. Infectious canine hepatitis: an "old" disease reemerging in Italy. Res Vet Sci. 2007;83:269-273.

Gocke DJ, Preisig R, Morris TQ, et al. Experimental viral hepatitis in the dog: production of persistent disease in partially immune animals. J Clin Invest. 1967;46:1506-1517.

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