



WEDNESDAY SLIDE CONFERENCE 2009-2010

Conference 5

7 October 2008

Conference Moderator:

Shannon M. Wallace, DVM, Diplomate ACVP

CASE I: 1096/02 (AFIP 2948705).

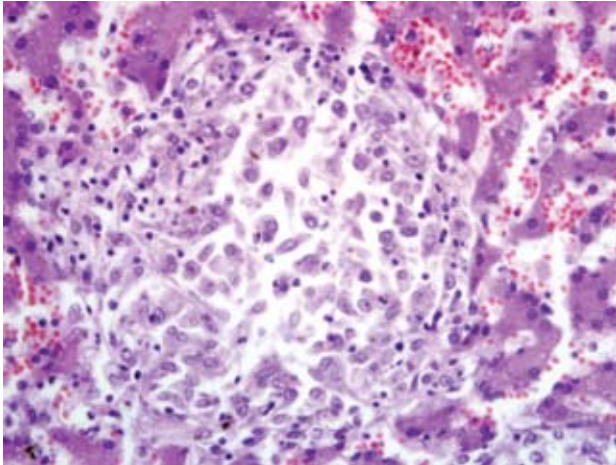
Signalment: 4-year-old, male beagle (*Canis familiaris*).

History: The dog presented with a two-month history of abdominal enlargement. Hepatomegaly was diagnosed. Two weeks prior to death, high fever (40.5 C), vomiting, diarrhea, weight loss, and lethargy were noticed. The dog arrived at the clinic severely weakened with bright yellow (jaundiced) mucous membranes and a tense abdomen. The patient died the next day.

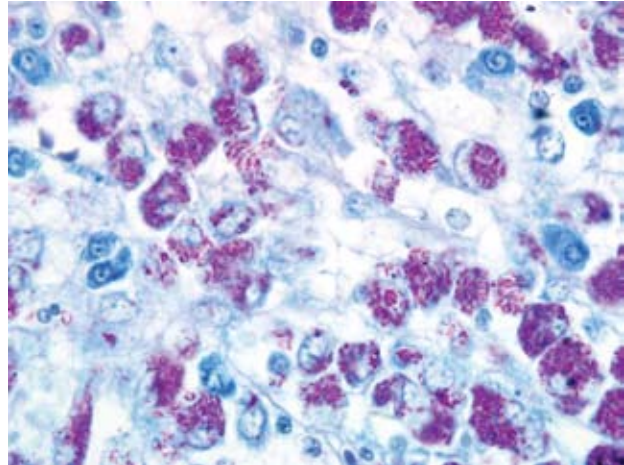
Gross Pathology: Severe jaundice and extreme enlargement of the lymphocentrum mesentericum craniale were the main postmortem findings. The lymph nodes showed a light brown to yellow cut surface with extensive necrosis; a differentiation between cortex and medulla was not possible. Other lymph nodes were moderately enlarged with a light brown cut surface. In vivo diagnosis of hepatomegaly was confirmed. The liver had a coarsely humped surface with multiple, confluent, light brown, not raised foci in the parenchyma of approximately one centimeter in diameter. Other findings included splenomegaly due to pulpy hyperplasia and a mild granulomatous nephritis.

Laboratory Results: Microbiological culture of the liver and kidneys revealed mycobacteria, which were identified as *Mycobacterium avium* by PCR and reverse hybridization.

Histopathologic Description: The histopathological examination of the liver, spleen, and lymph nodes of the lymphocentrum mesentericum craniale revealed an extreme infiltration of these organs with macrophages, which were characterized by a very large, euchromatic nucleus and a foamy, basophilic, granular cytoplasm, and sporadic giant cells of the Langhans type. The liver showed a severe interlobular, periportal, and intralobular infiltration with macrophages and a small number of lymphocytes causing almost total destruction of organ specific structures (**fig. 1-1**). Pressure atrophy of the surrounding liver tissue developed as a result of the extensive cellular invasion. Aside from the macrophage infiltration, the lymph nodes of the lymphocentrum mesentericum craniale showed central necrosis with multifocal calcification. Necrosis could not be found in other lymph nodes (e.g. lymphocentrum inguinale profundum, hepatic lymph nodes, lymphocentrum axillare), which were sinusoidally infiltrated with macrophages as well. Mild, circumscribed, predominantly perivascular infiltration with macrophages was present in both kidneys, the left



1-1. Liver, dog. Granulomas composed of epithelioid macrophages admixed with scant amounts of necrotic debris, bounded by fibroblasts and lymphocytes. (HE 400X)



1-2. Liver, dog. Epithelioid macrophages within granulomas contain many 1x5um acid fast bacilli. (Ziehl Neelsen 1000X)

ventricular myocardium and the lamina propria mucosae of the small intestine. The femoral bone marrow turned out to be myelopoetically active without any indication of osteomyelitis. The Ziehl-Neelsen stain revealed a massive presence of acid-fast rod-shaped bacilli in the macrophages infiltrating the liver, lymph nodes, spleen, kidneys, heart and intestine (fig. 1-2).

Contributor's Morphologic Diagnosis: Liver: Severe granulomatous hepatitis with an abundance of intrahistiocytic acid-fast rod shaped bacilli (Ziehl-Neelsen stain); etiology consistent with *Mycobacterium avium* (dog, beagle).

Contributor's Comment: Disease due to *Mycobacterium avium* occurs in mammals, especially as opportunistic infections, in the course of hereditary or acquired immune deficiencies. Generalized forms of tuberculosis as caused by *M. tuberculosis* or *M. bovis* have been rarely reported in dogs and cats in the last decades; but disseminated disease due to *M. avium* and other atypical mycobacterioses are described more often in the current literature.^{1,3-5,7}

A dog with *M. avium* infection was mentioned in 1979 by Friend et al.⁵ It is supposed that the infection can be caused by incorporation of infectious liver tissue of chickens or pigs. Both dogs and cats usually show a high resistance against *M. avium*.^{2-4,7} Therefore, hereditary immune deficiencies are thought to be responsible for the outbreaks described in the literature. Hereditary immune deficiencies are discussed in basset hounds³ and miniature schnauzers,^{4,7} which possibly go along with a high incidence of opportunistic infections in these breeds.

Such a breed associated immune deficiency is, to our knowledge, not described in beagles.

In the presented case, it was not possible to find out if the dog was fed potentially infectious material. The route of infection remains unclear. Because the bacteria are prominent in the liver, intestine, and its lymph nodes, but not in the lungs, an oral infection is presumed. The formation of a complete primary complex with a rapid lympho-hematological spreading of the bacteria in the course of an early generalization is supposed. The massive periportal, intra- and interlobular infiltration of the liver with pathogen-bearing macrophages matches the description of the typical liver tuberculosis in carnivores according to Pallaske.⁸ A similar morphology was seen in disseminated *M. avium* infection in dogs.^{2,4}

AFIP Diagnosis: Liver: Hepatitis, granulomatous, multifocal to coalescing, marked, with numerous intrahistiocytic acid-fast bacilli.

Conference Comment: Because of the extent to which the granulomatous infiltrate effaces normal hepatic architecture in this case, many participants considered a neoplastic or atypical histiocytic proliferation in their initial differential diagnosis. *Mycobacterium avium* and *M. intracellulare* are two separate species that result in very similar lesions, and are thus referred to as *M. avium-intracellulare* complex (MAC).⁶ These nontuberculous, nonpromatous mycobacteria are the most common etiologic agents in disseminated mycobacteriosis in dogs, although the disease remains uncommon overall.⁷ Interestingly, they are also the most common opportunistic mycobacteria isolated from localized cutaneous infections

in dogs and cats.⁶ The lesions in the intestine and lymph nodes in this case, as well as in previously-reported cases, bear striking resemblance to those seen in sheep and cattle with Johne's disease. This is not particularly surprising, given that the causative agent of Johne's disease is *M. avium* subsp. *paratuberculosis*. In humans, disseminated opportunistic mycobacteriosis is usually associated with immunosuppression due to AIDS, and in reported canine cases, immunosuppression has been suspected, though not unequivocally proven. An alternate hypothesis for the pathogenesis in cases where multiple littermates are affected is exposure to a common source, possibly perinatally, as occurs in Johne's disease.⁷

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CASE II: 05-0947 (AFIP 3101430).

Signalment: 3.5-week-old, female pixie-bob kitten (*Felis catus*).

History: This kitten died after a five-day clinical course characterized by coughing and gagging. She had been treated with antibiotics and subcutaneous fluids.

Gross Pathology: The right cranial and middle lung lobes and the left cranial and caudal lung lobes were dark red, collapsed and firm. There was a small amount of clear fluid in the thorax and abdomen.

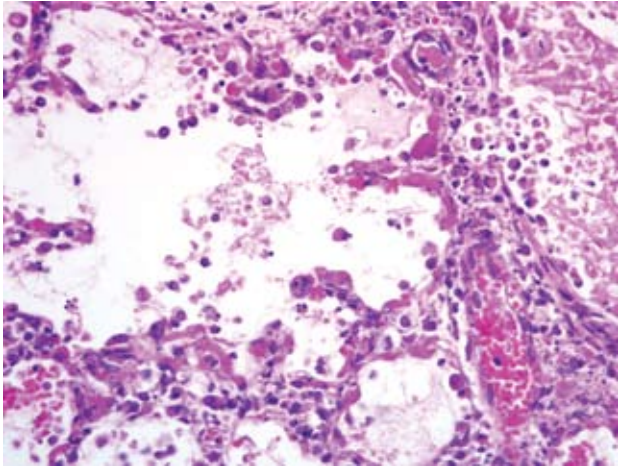
Laboratory Results: There was no bacterial growth from the lung. Viral isolation yielded feline herpesvirus-1.

Histopathologic Description: Sections of affected lung had multifocal areas in which alveolar spaces were filled with fibrin, cellular debris, edema, and hemorrhage associated with accumulations of pulmonary alveolar macrophages and neutrophils (**fig. 2-1**). Less affected alveoli were lined by plump type II pneumocytes. Alveolar septa were thickened by infiltration of mononuclear cells. Numerous sloughed epithelial cells within necrotic areas and lining alveoli had nuclei with peripheralized chromatin and containing amphophilic to eosinophilic nuclear inclusions. Other histologic lesions included erosive tracheitis, necrotizing lymphadenitis of the hilar lymph nodes and thymic atrophy. No viral inclusions were seen in any other tissues.

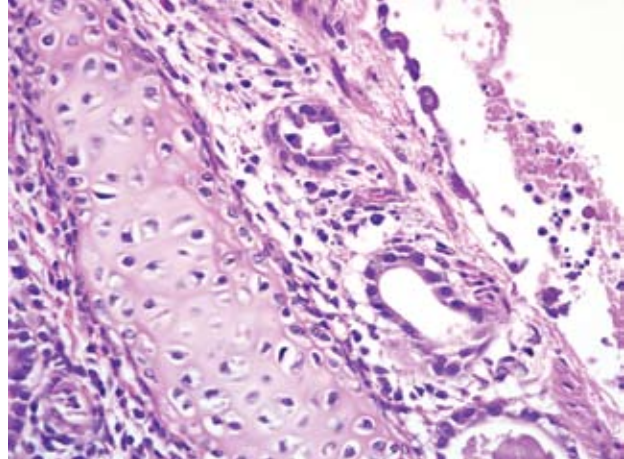
Contributor's Morphologic Diagnosis: Necrotizing interstitial pneumonia with epithelial intranuclear inclusions (FeHV-1).

Contributor's Comment: Feline herpesvirus 1 is an α -herpesvirus, the host range of which is generally restricted to domestic cats and wild felidae.² It is a double stranded DNA virus with a single serotype that is antigenically closely related to canine herpesvirus-1 and phocine herpesvirus-1. It does not persist for long periods in the environment so transmission must be by direct contact and exchange of ocular and nasal fluids. Like many herpesviruses, it grows best at low temperatures, so replication is usually restricted to the ocular and nasal tissues. Infected cats often become latent carriers that can re-shed the virus during periods of stress.^a

The classic disease associated with infection is 'feline rhinotracheitis,' most commonly manifested as upper respiratory disease with conjunctivitis in susceptible



2-1. Lung, cat. Alveolar septa are necrotic and replaced by brightly eosinophilic debris, or expanded by neutrophils and histiocytes. Alveoli contain many macrophages, neutrophils, and sloughed epithelial cells admixed with fibrin and edema. (HE 400X)

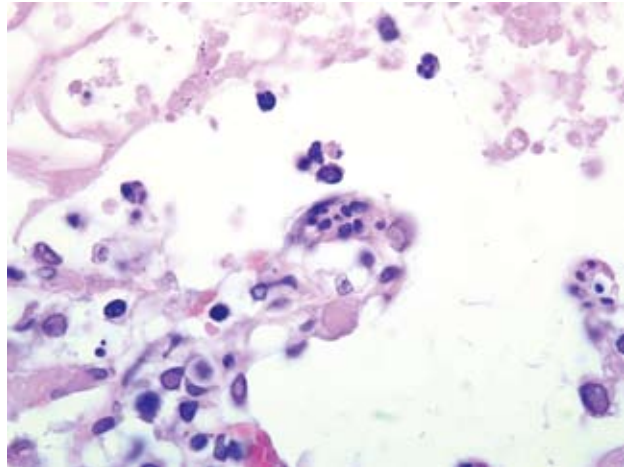


2-2. Lung, cat. Attenuated and necrotic bronchiolar epithelium overlain with fibrin and sloughed necrotic epithelium. The peribronchiolar interstitium is expanded by edema admixed with histiocytes, neutrophils, and fewer lymphocytes. (HE 400X)

kittens. More recently, the virus has been implicated in cases of chronic conjunctivitis and periocular skin disease in adult cats.⁵ Although abortion has been induced experimentally in pregnant queens by intravenous inoculation, it is not thought to occur with significant frequency as a natural disease.² Likewise, neonatal disease can be induced by exposure of kittens within the vaginal vault, but spontaneous cases of systemic disease in cats and kittens are rare.

Definitive diagnosis of herpesviral respiratory disease is often made clinically, but viral isolation from oropharyngeal swabs is possible if needed. The advent of PCR and in situ hybridization has made possible the implication of feline herpesvirus-1 in chronic keratoconjunctivitis and dermatitis as described above.⁵

Systemic disease characterized by interstitial pneumonia has been reported in kittens,³ and in one case a seven-month-old cat with severe glossal ulcers was reported to have died of systemic illness characterized by multifocal hepatic necrosis with typical nuclear inclusions in hepatocytes.⁴ In our case, a three-week-old Pixie-bob kitten had primary respiratory signs and at necropsy had lesions restricted to the lung. The diagnosis was suspected due to the presence of typical nuclear inclusions in pneumocytes and macrophages and was confirmed by viral isolation. Systemic herpesviral infections in kittens can be the result of immunosuppression, lack of protective antibodies or high pathogen load.² There are no reported genetic diseases of Pixie-bob cats that might predispose to severe viral infections. A possible scenario in this



2-3. Lung, cat. Intranuclear inclusions and few syncytial cells are observed. (HE 400X)

case would be stress-related recrudescence of FeHV-1 infection in the dam with transmission to a kitten with low protective antibodies. Chilling of a neonatal kitten to below body temperature may have allowed the virus to proliferate in systemic tissues.

AFIP Diagnosis: Lung: Pneumonia, bronchiointerstitial, necrotizing, subacute, multifocal to coalescing, marked, with intraepithelial intranuclear inclusion bodies and syncytia.

Conference Comment: There is significant section

variation with respect to the severity of the lesions in this case. In addition to the histopathologic changes described by the contributor, several conference participants observed necrosis of the bronchiolar epithelium and viral syncytia (figs. 2-2 and 2-3).

Alpha-herpesviruses specifically affecting the lung of domestic animals include feline herpesvirus 1 (feline viral rhinotracheitis), canine herpesvirus 1, gallid herpesvirus 1 (infectious laryngotracheitis), bovine herpesvirus 1 (infectious bovine rhinotracheitis), suid herpesvirus 1 (pseudorabies), caprine herpesvirus 1, equine herpesviruses 1 and 4 (abortion and rhinopneumonitis), and equine herpesvirus 5 (equine multinodular pulmonary fibrosis).⁽¹⁾ For a partial list of alpha-herpesviruses of veterinary importance, readers are referred to WSC 2007-2008, Conference 13, case II.

The contributor provided a succinct review of this entity. Conference participants also reviewed some less common clinical presentations of FeHV-1 infection, including ulcerative facial and nasal dermatitis, and stomatitis with eosinophilic infiltrates in cats and cheetahs.² For most participants, the differential diagnosis for necrotizing respiratory tract lesions in cats included feline calicivirus (FCV) infection, chlamydophilosis, and toxoplasmosis. When present, the characteristic herpesviral inclusions allow differentiation from FCV infection. However, herpesviral inclusions are only transient, and are usually absent after seven days post-infection. Herpesviruses are unique in that they elicit neutrophilic inflammation and fibrin exudation during respiratory infection, even in the absence of a secondary infection.² Feline calicivirus-induced pneumonia is generally interstitial in distribution, whereas FeHV-1 pneumonia is bronchointerstitial. Similarly, toxoplasmosis generally results in necrotizing multifocal to diffuse interstitial pneumonia, but the identification of intralésional protozoal cysts aids in making the diagnosis. *Chlamydomphila felis* is an important cause of conjunctivitis in cats and a minor upper respiratory pathogen, but not an important cause of pulmonary disease.¹

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<http://www.vetmed.wsu.edu/depts-vmp>

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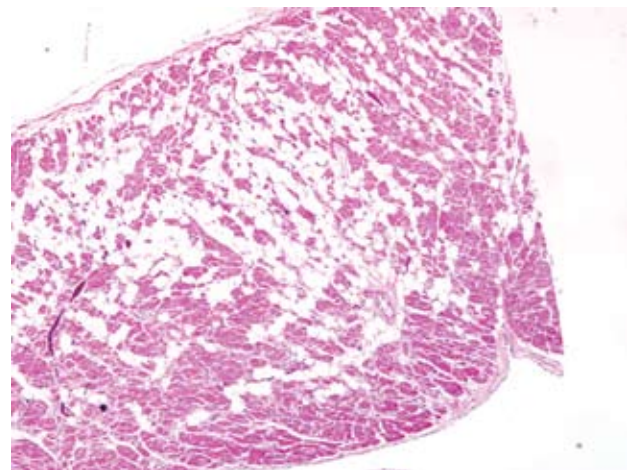
CASE III: 09-855 (AFIP 3134523).

Signalment: 6-year and 7-month-old, female, spayed boxer dog (*Canis familiaris*).

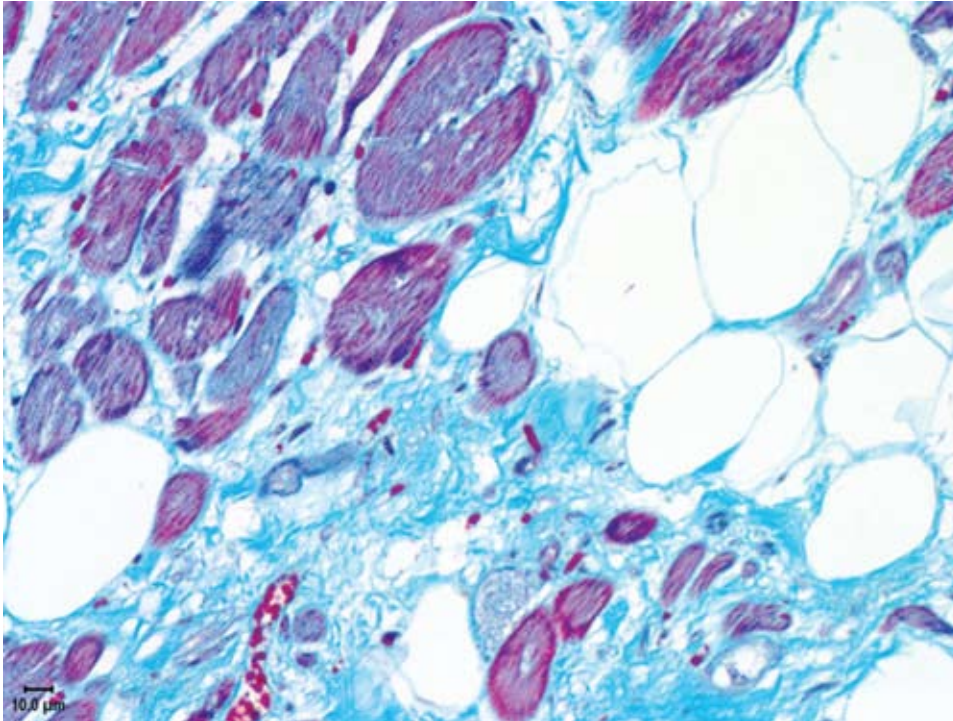
History: No history of prior illness, current on vaccinations and preventative medicine. Found dead two hours after vigorous exercise.

Gross Pathology: There were a small number (10-15) of scattered petechial hemorrhages on the epicardial surface of the heart.

Histopathologic Description: The right ventricular wall is severely infiltrated by individual and small aggregates of well differentiated adipocytes which replace approximately 50-60% of the cardiomyocytes (fig. 3-1).



3-1. Heart, dog. Approximately 50% of cardiac myocytes in the right ventricle are replaced by adipocytes, and many of the remaining myocytes are atrophied or degenerate. (HE 400X)



3-2. Heart, dog. Remaining cardiac myocytes are separated and surrounded by a moderate amount of fibrosis. (Masson's trichrome) Photomicrograph courtesy of Department of Population Health and Pathobiology College of Veterinary Medicine North Carolina State University 4700 Hillsborough Street Raleigh, NC 27606, sandra_horton@ncsu.edu.

There is multifocal moderate atrophy of the remaining cardiomyocytes and regionally extensive interstitial fibrosis (**fig. 3-2**). These changes are most severe in the subepicardial region of the ventricular wall. The right atrium and interventricular septum are similarly, but less severely, affected.

Contributor's Morphologic Diagnosis: Heart: Chronic moderate myocardial atrophy and interstitial fibrosis with replacement by adipocytes.

Contributor's Comment: These histologic findings are consistent with arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a variant of dilated cardiomyopathy (DCM), which occurs in boxer dogs, cats and humans. It is characterized histologically by severe myocyte atrophy in the right ventricular free wall and replacement by adipocytes and/or fibrous tissue. Replacement extends from the epicardial surface and extends towards the endocardium. Occasionally, the left ventricle and interventricular septum may also be involved.^{1,5-7} Two variants exist: fatty and fibrofatty forms. The fatty form consists of multifocal regions of adipocyte replacement within the right ventricular wall accompanied by a mild interstitial fibrosis. The fibrofatty form is characterized by focal-diffuse regions of myocardial replacement by adipose tissue and marked fibrosis.¹ The disease in dogs closely parallels that seen in humans; loss of right ventricular myocytes with replacement by fat or fibrofatty tissue is considered the pathologic hallmark

of human ARVC.¹ Clinical signs of ARVC may include ventricular arrhythmias, syncope, heart failure or sudden death. A spontaneous form of ARVC is also seen in cats, although unlike in dogs and humans, sudden death is not a feature of the disease.^{3,4}

ARVC is thought to be transmitted as an autosomal dominant trait in both boxer dogs and humans, although an autosomal recessive trait has also been identified in humans. In humans, mutations in the genes coding for various intercellular adhesion proteins, components of the sarcoplasmic reticulum calcium channel and cytokines have been implicated in the pathogenesis of ARVC.² To date, published reports of homologous genes in the dog have failed to identify equivalent mutations.^{8,10} However, a seven base pair deletion within the non-coding regulatory sequence of a calcium modulating gene on chromosome 17 has recently been identified as responsible for ARVC in boxer dogs.⁹ Although precise information regarding this mutation has not yet been released into the public domain, Washington State University College of Veterinary Medicine now offers a genotyping service for canine ARVC (<http://www.vetmed.wsu.edu/deptsVCG/Boxer/test.aspx>).

AFIP Diagnosis: Heart: Cardiomyocyte degeneration, necrosis, and loss, multifocal, marked, with fibrofatty infiltration.

Conference Comment: There is some variation

within the sections, with most participants' slides having a predominantly fatty infiltrate, while in a few slides, adipocytes are accompanied by a small amount of fibrosis (i.e. fibrofatty infiltrate) and rarely, a mononuclear cell infiltrate. This is interesting considering the sudden death of the dog in this case, because in one study of 23 boxer dogs with ARVC, of the nine dogs that died suddenly, all had myocarditis in the left and/or right ventricle, and six had the fibrofatty form. Of the 14 dogs with ARVC that did not die suddenly, only seven had myocarditis, and only two had a fibrofatty infiltrate. Myocarditis may lead to arrhythmias that cause sudden death. In cats, the fibrofatty form predominates, but sudden death is not a feature of ARVC in felids.¹ Dilated cardiomyopathy (DCM), of which ARVC is one variant, is the most common canine cardiomyopathy, with a number of large- and giant-breed dogs being predisposed. An infantile form in Portuguese water dogs is inherited as an autosomal recessive trait, while an X-linked recessive gene is suspected in Great Danes. Nutritional deficiencies (e.g. taurine and carnitine deficiency) and endocrinopathies (e.g. hypothyroidism) have also been associated with DCM. Less common in dogs are hypertrophic cardiomyopathy, characterized by disproportionate interventricular septal thickening and myofiber disarray, and canine X-linked muscular dystrophy, a disease of golden retrievers characterized by subendocardial interstitial fibrosis.⁶

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CASE IV: N2009-23-3 (AFIP 3135081).

Signalment: 13-year-old female axis deer (*Axis axis*).

History: This axis deer was found dead without any premonitory signs. The keepers had reported repeated episodes of dominant behavior and aggression from other deer in the group.

Gross Pathology: At necropsy, the abdominal cavity was filled with 1.5 to 2 gallons of frank blood with many free-floating blood clots. Several of these clots were loosely adhered to the serosal surfaces of the viscera and to the hepatic capsule. Approximately 60-75% of the liver was effaced and replaced by a soft, yellow/tan, lobulated, partially hemorrhagic, nodular mass (**fig. 4-1**). Blood clots and a portion of the omentum were loosely adhered to the central area of the mass. Randomly scattered throughout all lung lobes were numerous, up 1.5 cm diameter soft, yellow/tan, nodules that occasionally are surrounded by a rim of dark red discoloration (hemorrhage). The cranioventral lung lobes were slightly "meaty" and mottled dark red (congestion). All cut sections of the lungs floated readily in formalin except the cranioventral portions, which floated just beneath the surface. This deer was also



4-1. Hepatocellular carcinoma, liver, Axis deer. Approximately 60-75% of the liver is replaced by a soft, yellow/tan, lobulated, partially hemorrhagic, mass. Photograph courtesy of Wildlife Conservation Society Global Health Program – Pathology 2300 Southern Boulevard Bronx, NY 1046 crodriguez@wcs.org.

in thin body condition and there were several areas of bruising along the thoracic and abdominal body wall.

Histopathologic Description: Participants that review slide A will have a section of lung from caudal lobes and those that receive slide B will have a section of lung from the cranioventral lobe. All slides have sections of the liver.

Liver: Approximately 40% of the preexistent hepatic parenchyma is effaced, compressed and replaced by a focally extensive, unencapsulated, vaguely lobulated, infiltrative nodular mass. The mass is composed of irregular cords and trabeculae of polygonal cells with discrete cytoplasmic borders, abundant finely granular cytoplasm and a single to occasionally multiple round to elongated vesicular nuclei with coarsely clumped chromatin and one to multiple prominent nucleoli (fig. 4-2). Neoplastic cells display marked anisocytosis and anisokaryosis, marked nuclear atypia and a low mitotic rate (1-2 mitoses per 10 40X fields). Separating the neoplastic cells into lobules and nests is a pervasive, densely cellular fibrous connective tissue stroma that occasionally contains atrophied ductular structures. Within central areas of the mass there are regions of loss of cellular detail and differential staining that are replaced with cellular and karyorrhectic debris (necrosis). Peritumoral hepatic cords are compressed and there is variable congestion and hemorrhage (not present in all slides). Single and small clusters of pigment-laden

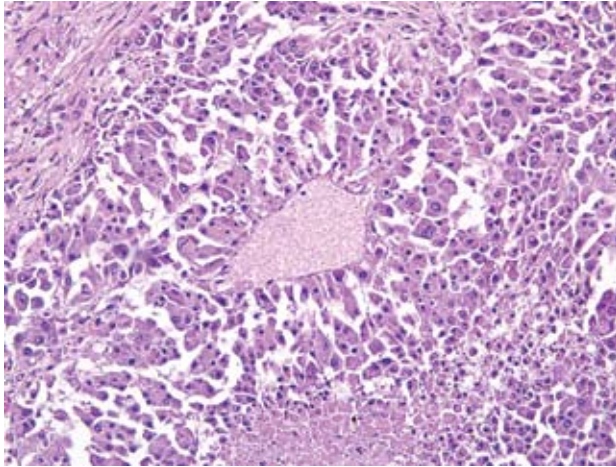
macrophages (hemosiderophages) are present throughout the section both within the sinusoids as well as associated with portal regions.

Lung: Effacing approximately 30% of the pulmonary tissue is a focally extensive, unencapsulated, vaguely lobulated, infiltrative nodular mass. The neoplastic cells display morphologic features consistent with the neoplastic cells previously described in the liver. In addition, variably prominent throughout the sections, clusters of neoplastic cells are present within the lumen of vascular structures (neoplastic emboli) and often extend into and adjacent alveolar spaces (fig. 4-3). In sections of lung from the cranioventral lobes (slide B) there is marked hemorrhage and edema that obscure most of the alveolar spaces accompanied by peribronchiolar, intraluminal and intraalveolar dense aggregates of viable and degenerate neutrophils and macrophages that contain ingested erythrocytes as well as coarse, golden yellow pigment granules (hemosiderin).

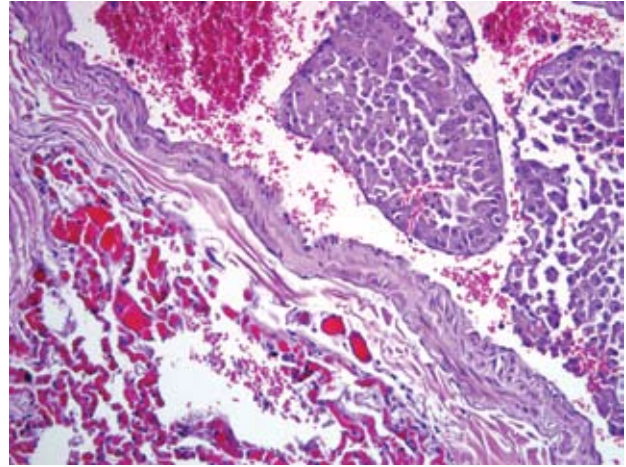
Contributor's Morphologic Diagnosis:

1. Liver: Hepatocellular carcinoma, pseudoglandular, regionally extensive, severe with fibrosis, intratumoral necrosis and perilesional parenchymal compression and hemorrhage.
2. Liver: Hemosiderosis, chronic, multifocal, mild to moderate.
3. Lung (all slides): Hepatocellular carcinoma, metastatic, regionally extensive, severe with intratumoral necrosis and hemorrhage and multifocal vascular tumor emboli.
4. Lung (slide B): Pneumonia, bronchointerstitial, acute to subacute, regionally extensive, moderate to severe with regionally extensive hemorrhage, edema, fibrin, erythrophagocytosis and hemosiderin deposition.

Contributor's Comment: Hepatocellular carcinomas, although relatively uncommon, have been reported in most domestic and in several wild animal species,¹⁻¹⁰ with some sources citing the highest incidence in ruminants, particularly sheep,² and others, in dogs.¹ These tumors are often massive and may involve one or more entire lobes of the liver.^{1,2} The left lateral lobe is reported to be more commonly affected.¹ This tumor is characterized histologically by disorganized arrays of neoplastic hepatocytes but their morphology can vary greatly, from well differentiated hepatocytes to markedly anaplastic and bizarre cells. Based on their histologic pattern, hepatocellular carcinomas can be classified as trabecular, adenoid (or pseudoglandular) and solid.^{1,2,10} Trabecular carcinomas are composed of variably wide (up to 20 cells thick) cords of hepatocytes with minimal supportive connective tissue stroma. In these tumors, neoplastic hepatocytes may or may not exhibit features of malignancy and differentiating between a well-differentiated hepatocellular carcinoma



4-2. Hepatocellular carcinoma, liver, Axis deer. Effacing up to 50% of the section is a neoplasm composed of polygonal cells which occasionally recapitulate hepatic lobules. There is marked anisokaryosis and anisocytosis, and there are multifocal binucleate neoplastic cells. (HE 200X)



4-3. Hepatocellular carcinoma, lung, Axis deer. Multifocally, neoplastic cells are found within pulmonary vasculature. (HE 200X)

and a hepatocellular adenoma can present a daunting challenge.^{1,2} Adenoid, or pseudoglandular tumors exhibit the formation of irregular acini that may develop a lumen containing proteinaceous fluid. Discriminating between a well-differentiated carcinoma with a pseudoglandular pattern and a cholangiocarcinoma may also be very challenging.¹ Solid carcinomas are often poorly-differentiated and are composed of sheets of pleomorphic neoplastic cells with no apparent pattern of distribution. In less well-differentiated neoplasms, cellular and nuclear variability can be marked and often giant cells with karyomegalic forms or multiple nuclei can be found.¹

Intrahepatic metastases are common and vascular, rather than lymphatic invasion, is more typical in these tumors.^{2,10} Metastatic spread to the lungs and to lymph nodes within the cranial abdomen is also a feature of this neoplasm, as is invasion of the hepatic capsule and seeding of the peritoneal cavity.^{1,2,10} Rupture of these neoplasms can occur spontaneously¹⁰ and, as in this case, can result in a fatal intraabdominal hemorrhage; however, rupture of the tumor in this deer may have resulted from aggressive or dominant behavior between individuals in the herd. In addition, at the time of the necropsy there was evidence of mild aspiration pneumonia (not represented in all slides) that may have also been the result of repeated harassment or trauma by other members of the herd in the hours to days prior to death.

The etiology of most hepatocellular carcinomas is unknown. Numerous chemical compounds used in industrial and/or

experimental settings have been linked to the development of hepatic neoplasia in humans and laboratory animals, but significant exposure of these to domestic and wild animal species is unlikely.¹ Naturally occurring toxic compounds, such as aflatoxins, pyrrolizidines and nitrosamines, and infectious agents, such as hepatitis B viruses, woodchuck hepatitis virus and *Helicobacter* spp. in some strains of mice, have been implicated in hepatic carcinogenesis.¹ Dietary factors and availability of foraging substrates are also suspected of playing a role in the increased incidence of hepatocellular carcinomas within geographically distinct populations of roe deer (*Capreolus capreolus*) in Britain.^{3,7}

In non-domestic species, hepatocellular carcinomas have been reported in black-tailed prairie dogs (*Cynomys ludovicianus*) and other members of the Sciuridae family, in which a viral etiology is suspected.⁵ Nearly all woodchucks (*Marmota marmota*) infected with the woodchuck hepatitis virus are known to develop hepatocellular carcinoma.¹ In cervids, hepatocellular carcinomas have been reported in roe deer (*Capreolus capreolus*) and white-tailed deer (*Odocoileus virginianus*).^{3,7,8} Other neoplasms reported in cervids include spontaneous abomasal and uterine adenocarcinomas in an elk (*Cervus elaphus nelsoni*)⁴, cardiac rhabdomyosarcoma in a juvenile fallow deer (*Dama dama*)⁶, and uterine adenocarcinoma in a sika deer (*Cervus nippon*).⁹

AFIP Diagnosis: 1. Liver: Hepatocellular carcinoma. 2. Lung: Hepatocellular carcinoma, metastatic.

Conference Comment: The contributor provides an excellent review of hepatocellular carcinoma in domestic and non-domestic species. Noteworthy, the lung and liver are the most common organs for metastasis of malignant neoplasms, and most hepatic neoplasms are not of primary liver origin, but rather represent metastases from other organs. In addition to hepatocellular carcinoma, primary hepatic neoplasms include hepatocellular adenoma, cholangiocellular adenoma and carcinoma, carcinoids, and mesenchymal neoplasms, such as fibrosarcoma, leiomyosarcoma, osteosarcoma, and hemangiosarcoma. Hepatocellular neoplasms are differentiated from hyperplastic nodules by their paucity of portal tracts, which are retained in the latter. Hepatocellular adenomas are most common in young ruminants, and are usually single masses composed of uniform plates of well-differentiated hepatocytes that compress and orient at right angles to adjacent normal hepatocytes. As noted by the contributor, hepatocellular adenomas may be difficult to distinguish from well-differentiated hepatocellular carcinomas of the trabecular type. In contrast, cholangiocellular adenomas are most common in cats, and may form large, cystic structures lined by flattened epithelium. Cholangiocellular carcinomas may be well- or poorly-differentiated, and often appear umbilicated on gross examination. They are usually firm as a result of a robust scirrhous response, and the metastatic rate to the lungs and/or abdominal lymph nodes is high. Carcinoids arise from neuroendocrine cells of the biliary epithelium, may be intrahepatic or extrahepatic, and may stain positively with neuroendocrine markers, such as chromogranin A.^{1,2}

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