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Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
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Conference Moderator: Dr. Michael Topper, DVM, DACVP, PhD
Gene Logic
Gaithersburg, Maryland

CASE I – 1178/03 (AFIP 2948699)

Signalment: Four month-old, male, New Zealand White rabbit.

History: This rabbit was one of 20 rabbits in an experimental study inducing chronic cardiomyopathy. Doxorubicin (3 mg/kg) was given intravenously in the lateral ear vein of three month-old male rabbits once a week for a six week period. The presented animal died after the fourth dose and was autopsied.

Gross Pathology: Mild alopecia was visible at the neck. There was 15 ml of watery fluid in the thorax. The myocardium was grayish-brown and the left ventricle of the heart was mildly dilated. The lungs showed moderate diffuse acute emphysema and edema. The testes were small and soft, and bone marrow was light-red but of normal consistency. The spleen and lymph nodes were light-brown, small and inactive. The gastrointestinal tract showed moderate diarrhea. The liver, kidneys and brain were without any specific morphological lesions.

Contributor's Morphologic Diagnoses: 1. Heart: Myocardial degeneration, eosinophilic and vacuolar, diffuse, with mild fibrosis, and multifocal, mild, mononuclear inflammation.
2. Bone marrow: Hypocellularity, diffuse, severe.
3. Testis: Degeneration and atrophy of the seminiferous tubular epithelium, diffuse, moderate.
4. Skin: Epidermal and adnexal atrophy, diffuse, moderate. (not submitted)
5. Intestine: Atrophy of the intestinal mucosa, moderate, with diffuse mild lymphoplasmacytic infiltration. (not submitted)
6. Lymph nodes, spleen: Hypocellularity, moderate. (not submitted)

Contributor's Comment: Anthracycline antibiotics, such as doxorubicin (adriamycin), epirubicin and daunorubicin, are effective anti-neoplastic agents which are widely used in cancer chemotherapy. However, administration of these agents is associated with a dose-related cardiomyopathy,[1] atrophy of hematopoietic tissues,[1] nephrotoxicosis,[2] and atrophy of skin and testes[1,3] as well as intestinal alterations.[4]

Cellular mechanisms of anthracyclines inducing heart failure are multifactorial and include local release of vasoactive substances,[5] cytotoxic effects of local free radicals,[6] inhibition of nucleic acid and protein synthesis,[7] and disturbed Ca^{2+} metabolism in cardiomyocytes.[8]

Acute doxorubicin toxicity is reflected by increased cytoplasmic eosinophilia and mild to moderate vacuolization of cardiomyocytes. Ultrastructurally, numerous vacuoles, swollen mitochondria with "onion ring" shaped cristae, and swollen sarcoplasmic reticulum occur. Myofibrillar loss as well as separation of intercalated discs and dilatation of the sarcotubular system is described.[3] In later stages small numbers of T-lymphocytes and histocytes surround the degenerating/necrotic myocytes[9] and interstitial fibrosis[1] is evident. Chronic effects may occur several weeks or months after repetitive exposure of cardiomyocytes to anthracycline. In humans, cardiovascular signs indicative of chronic cardiotoxicity include severe congestive heart failure.[10]

Further pathological systemic side effects due to anthracycline administration are described in organs with high turn over rate of cells leading to bone marrow depression, alopecia and atrophy of the skin, and testicular atrophy[1] as observed in the present case. Additionally, in long term studies at about 17 weeks, necrosis and calcification of the liver, skeletal muscles and pancreas were observed.[1]

The lesions of the present case are typical findings induced by anthracyclines.[3,11] Since it is often used in experiments studying therapeutic models of cardiomyopathy, intensive investigations of this cardiac disease are available in literature. However, the effects on other organs are described sparsely[3,11] but may be responsible for the death of animals during experiments due to diarrhea, hemorrhagic diathesis and opportunistic infections.

AFIP Diagnoses: 1. Heart: Myocardial vacuolar degeneration, necrosis, and loss, diffuse, mild to marked, with multifocal mild fibrosis, New Zealand White, rabbit, lagomorph.
2. Bone marrow, hematopoietic cells: Hypocellularity, diffuse, marked.
3. Testis, spermatogenic epithelium: Degeneration and atrophy, diffuse, severe.

Conference Comment: The contributor provides a thorough overview of the dose-dependent cardiotoxicity of adriamycin. Both nutritional and toxic myopathies tend to result in degeneration and necrosis with little to no inflammation. However, if the animal survives long enough, inflammation may be present in response to the necrosis. Common causes are listed below:[12,13]

Disorder	Cause	Primary Species Affected
Ionophore toxicity	Monensin	Horses, pigs
	Lasalocid	Many
Plant toxicity	Cardiac glycosides (*Nerium oleander*)	Many
	Lantana camara	Small ruminants
	Gossypol	Young ruminants, pigs
	Cassia occidentalis	Many
	Hairy Vetch (*Vicia villosa*)	Many
	Calcinogenic plants (*Cestrum diurnum*) (*Trisetum flavescens)* (*Solanum malacoxylon*)	Many
Nutritional	Vitamin E/Selenium deficiency	Many
Other	Blister beetle (*Epicauta* sp.)	Horses

Many conference attendees considered nutritional causes of cardiomyopathy. Vitamin E and selenium deficiency is well recognized and has been described in many species, including rabbits. However, with rigid quality control standards for commercial feed, nutritional myopathy is relatively rare in laboratory colonies. Occasionally researchers prepare specialized diets for specific research protocols, and deficiencies can result from errors in these formulations. Affected rabbits may present with stiffness and muscle weakness, infertility, or increased neonatal mortality. At necropsy, the musculature, especially of the diaphragm, paravertebral regions, and the hind limbs, may be pale with mineralized streaks. Microscopically, there is typically hyaline degeneration of affected myofibers and clumping and mineralization of the sarcoplasm. Interstitial fibrosis frequently occurs in lesions of longer duration.[14]

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CASE II – 420230 (AFIP 2948690)

Signalment: Mixed breed dog, approximately 6 weeks of age.

History: Died acutely without any clinical signs.

Gross Pathology: The pup was in good to moderate body condition. The most prominent findings were ecchymoses in the mucosa of the digestive tract. The liver was congested and slightly enlarged. The gallbladder wall was edematous. The spleen and lymph nodes were edematous and congested.

Contributor's Morphologic Diagnosis: Liver: Hepatitis, necrotizing, centrilobular, severe, with occasional intranuclear inclusion bodies consistent with Canine Adenovirus type 1 (CAV –1), mixed breed dog.

Contributor's Comment: Infectious canine hepatitis (ICH) caused by canine adenovirus -1 (CAV-1) was recognized as a specific viral disease of dogs in 1947.[1] The virus is a medium-sized DNA virus without a lipoprotein envelope. There is antigenic relationship between CAV-1 and CAV-2, and they provide cross-protective immunity.[2] Infection can cause severe disease in dogs, other canids, and also in bears (Family *Ursidae*).[3] The virus is ubiquitous, and is excreted in the urine of affected dogs for long periods of time. As with other adenoviruses, CAV-1 is resistant to environmental inactivation with chemicals such as chloroform, ether, acid and formalin. The virus survives for days at room temperature and remains viable for months at temperatures below 4° C. CAV-1 is inactivated after 5 minutes at 50 to 60° C. Chemical disinfection is successful using iodine, phenol and sodium hydroxide.[3]

Vaccination has greatly reduced the incidence of the disease and it is now rare in many countries. Infection with CAV-1 probably occurs in nature via the oral route.[4] The incubation period is from 4 to 7 days. Virus multiplication occurs first in the tonsils leading to tonsillitis and local lymphadenitis, and the infection reaches the blood via the thoracic duct. Viremia lasts between 4 to 8 days after infection and results in rapid dissemination of the virus to other tissues and body secretions, including saliva, urine and feces.[3]

The clinical signs caused by CAV-1 infections are due to cellular damage as a result of direct effects of viral replication. The virus of ICH has a special tropism for endothelium, mesothelium and hepatic parenchyma, and it is injury to these tissues that is responsible for the pathologic features of edema, hemorrhage and hepatic necrosis.

AFIP Diagnosis: Liver: Hepatocellular necrosis and loss, centrilobular and midzonal, diffuse, with marked congestion and hemorrhage, and basophilic hepatocellular intranuclear inclusion bodies, mixed-breed, dog.

Conference Comment: As mentioned by the contributor, due to vaccination infectious canine hepatitis is now rare in many countries in which it was once endemic.

Clinically, affected dogs may have inapparent infection, mild illness, or severe disease with vomiting, melena, high fever, abdominal pain, blanched mucus membranes with petechia, and occasionally icterus.[3] Virus-induced endothelial damage may lead to disseminated intravascular coagulation and hemorrhagic diathesis.[5] In the peracute form of the disease, the animal may be found dead without previously observed clinical signs.[3] Some recovering dogs will develop an immune complex uveitis (type III hypersensitivity) resulting in unilateral or bilateral corneal edema (blue eye).[5]

The virus has a special tropism for endothelium, mesothelium, and hepatic parenchyma, resulting in gross and microscopic lesions due to cellular injury. Grossly, the classic lesion is marked edema of the gallbladder wall. If the edema is mild, it may only be evident in the attachments of the gallbladder. The gallbladder may also be darkened by intramural hemorrhages.[3] Other lesions include edema and hemorrhage of the superficial lymph nodes, linear (paintbrush) hemorrhages on the serosa of the stomach, [3] widespread petechia and ecchymoses, fluid in serous cavities, fibrin strands on the surface of an enlarged, turgid and friable liver, or small foci of hepatocellular necrosis.[5] Gross lesions in other organs are inconsistent. Histologically, there may be hemorrhages in many tissues due to the endothelial tropism and the resultant destruction. At low magnification, the histologic changes in the liver appear similar to those caused by acute hepatotoxins producing a prominent centrilobular (periacinar) pattern. The virus is known to produce large, amphophilic to basophilic, solid, intranuclear inclusion bodies that often have a "smudgy" appearance and fill the nucleus. They may be found in hepatocytes, endothelial cells, Kupffer cells, renal tubular epithelium, bronchial epithelium, and primitive reticulum cells.[3] Ultrastructurally, adenoviruses are nonenveloped, 70-90 nm, icosahedral particles that form characteristic paracrystalline arrays within the nuclei of affected cells.[6]

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CASE III – 200404 (AFIP 2942014)

Signalment: Three-year-old, female, Holstein, bovine.

History: This animal was kept in a herd of cattle experimentally infected with bovine leukemia virus (BLV). Clinical examination did not reveal any abnormalities.

Gross Pathology: None reported.

Laboratory Results: BLV serology: positive; nested PCR positive for BLV-proviral DNA

Hematology

Hct	24.0	%
Hb	10.0	g/dl
RBC	6.1	x $10^6/\mu l$
MCV	39.6	fl
MCH	16.5	pg
MCHC	41.7	%

RBC morphology: normal (echinocytes)

Platelets:	347.0	x $10^3/\mu l$
MPV:	7.6	fl

WBC:	16.9	$x10^3/\mu l$	H
Segm. Neu:	1.1	$x10^3/\mu l$ (6.0 %)	
Band Neu:	0.1	$x10^3/\mu l$ (1 %)	
Lymp:	14.5	$x10^3/\mu l$ (86 %)	H
Mono:	0.9	$x10^3/\mu l$ (5.5 %)	
Eos:	0.3	$x10^3/\mu l$ (1.5 %)	
Baso	0.0	$x10^3/\mu l$ (0 %)	
WBC morphology:	normal		

Contributor's Morphologic Diagnosis: Pappenheim's stained peripheral blood smear: Parasitemia, numerous flagellated protozoa, etiology consistent with *Trypanosoma sp*.

Contributor's Comment: The blood smear contains on average in each 400x field two spindle-shaped curved protozoan organisms that are between erythrocytes and sometimes in proximity to aggregated platelets. The 30-35 μm long protozoa are characterized by tapered ends, an undulating membrane with a flagellum up to 30 μm long, a central nucleus and a large marginal kinetoplast. These morphological features, and the fact that they were isolated from a cow within Germany, are most likely consistent with *Trypanosoma (Megatrypanum) theileri.* These protozoan parasites occur with worldwide distribution and can be isolated from 50 to 70% of blood cultures from clinically healthy cattle. However, singular cases of higher parasitemia, serious clinical disease or even death are recorded in cattle severely stressed from concurrent disease or in newborn calves.[1] Parasitemia is common in cattle herds with concurrent BLV-infection.[2] *T. theileri* is transmitted mechanically by many biting fly species (*Tabanus*, *Haematopota*) and probably by ticks (*Rhipicephalus*, *Boophilus*, *Ixodes*). In general, the parasitemia is very low, and the trypanosomes are found incidentally in smears of blood or blood cell cultures. In many cases, detection is only possible after repeated blood culture (blood-agar-plates, Eagle's medium, BHJ-agar with 10% rabbit blood and incubation at 28 °C or 37 °C). Therapeutic approaches are usually not necessary. The observed lymphocytosis in this case is related to the experimental infection of this animal with BLV and was shown by flow cytometry to be caused by an expansion of CD5+ sIgM+ B-lymphocytes. This is considered as characteristic for the persistent lymphocytotic (PL) stage of the disease.

AFIP Diagnosis: Peripheral blood smear: Trypomastigotes, numerous, and a relative lymphocytosis, Holstein, bovine.

Conference Comment: *Trypanosoma theileri* is classified within the phylum Sarcomastigophora, class Zoomastigophorea, order Kinetoplastida, family

Trypanosomatidae, genus *Trypanosoma*, subgenus Megatrypanum. It is one of the largest mammalian trypanosomes and is commonly an incidental finding in clinically healthy cattle, but may cause serious disease in immunocompromised animals.[3]

Blood sucking arthropods, especially tabanid flies such as the common horsefly, serve as vectors. Following ingestion during a blood meal, trypomastigotes undergo cyclic development in the insect's gut. The infective stages are then excreted during subsequent feedings and enter the host through the bite wound or abrasions in the skin.[4] Other *Trypanosoma* spp. are listed below:[3,5]

Organism	Transmission	Species	Disease / Lesions
T. cruzi	Reduviid bugs	Dogs	"Chagas' disease"; myocarditis
T. brucei	Tsetse fly	Ruminants	"Nagana disease"; anemia
T. congolense	Tsetse fly	Ruminants	"Nagana disease"; anemia
T. vivax	Tsetse fly	Ruminants	Anemia
T. evansi	Biting fly	Many	"Surra"; edema, emaciation
T. equinum	Biting fly	Horses	"mal de Caderas"
T. equiperdum	Coitus	Horses	"Dourine"; genital plaques
T. gambiense	Tsetse fly	Humans	"African Sleeping Sickness"
T. rhodesiense	Tsetse fly	Humans	"African Sleeping Sickness"
T. cervi	Horsefly	Deer	Nonpathogenic
T. melophagium	Sheep ked	Sheep	Nonpathogenic

As mentioned by the contributor, *T. theileri*, may be pathogenic in animals that are stressed or otherwise immunocompromised. This animal was experimentally infected with bovine leukemia virus (BLV), the cause of enzootic bovine lymphoma. BLV is a retrovirus and has a high incidence in dairy cattle. Transmission is primarily horizontal via blood-sucking arthropods or by fomites. Clinical expression peaks at 6-8 years post-infection with animals often presenting with enlargement of one or more superficial lymph nodes. Clinical signs reflect the location of the lesions: unilateral or bilateral exophthalmus with involvement of retrobulbar lymphoid tissue; diarrhea with gastrointestinal involvement; congestive heart failure if the heart, most commonly the right atrium, is affected; or posterior paresis or paralysis with nervous system involvement. In addition, animals may have lesions in the liver and spleen with involvement of the bone marrow and leukemia during the terminal stages of the disease. A persistent lymphocytosis develops in approximately 30% of animals and may occur without, or prior to, clinical expression of the disease.[6]

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CASE IV – N04-46 (AFIP 2937499)

Signalment: 8-year-old, female, mongrel dog, canine (*Canis familiaris*).

History: This animal was presented with a one-week history of hematuria and mild constipation. A mass was palpated in the caudal abdomen during physical examination. A pneumocystogram revealed a tumor within the urinary bladder. The growth was located on the ventral surface near the trigone area. It was removed surgically and submitted for examination.

Gross Pathology: A papillary mass measuring 5.5 x 5 x 2.5 cm was submitted for histological assessment. The papillary projections were gray white and intermixed with blood clots. The bladder wall underneath the tumor was thickened and sclerotic.

Laboratory Results: A complete blood count revealed lymphocytosis, granulocytopenia, and polycythemia.

Lymphocytes = 57% (10.0-40.0)
Granulocytes = 37.7% (50.0-80.0)
RBC = 9.24 m/mm^3 (5.5-8.5)
MCV = 75.1 fl (58.0-73.0)
Hct = 69.3% (35.0-55.0)
Hb = 19.6 g/dl (10.0-18.0)

Contributor's Morphologic Diagnosis: Urinary bladder: Transitional cell carcinoma, papillary, infiltrating.

Contributor's Comment: Sections of the submitted tissue reveal multiple, tall papillary growths covered by multiple layers of closely-packed, columnar to polygonal cells supported by thin stalks of fibrovascular connective tissue. Tumor cells have moderate amounts of pale eosinophilic, often vacuolated cytoplasm, with well-defined cell borders. Tumor cell nuclei are round to oval, euchromatic, with finely granular chromatin, usually single prominent nucleoli, and show moderate anisokaryosis. Mitotic figures are common (1-3 per random 40x field). Small clusters of neoplastic cells infiltrate into the stalks of the tumor, the lamina propria, submucosa, and muscle layers of the bladder wall. Multifocally, variably sized aggregates of lymphocytes mixed with lesser numbers of eosinophils are scattered throughout the stalks and lamina propria. Gross and histomorphologic features of this case are characteristic of the papillary and infiltrating variant of transitional cell carcinoma.

Neoplasia of the urinary bladder is common in dogs, relatively frequent in cats, and rare in all other species. Cattle rarely develop urinary bladder tumors spontaneously but have a high prevalence (as high as 25%) in endemic areas where bracken fern (*Pteridium* spp.) grows.[1] The etiology of bladder cancer in dogs is unknown. However, topical insecticides containing inert petroleum products commonly used for fleas and ticks, in addition to obesity, appear to increase the risk of bladder cancer in this species. Tryptophan, its metabolites, and the cytotoxic drug cyclophosphamide have also been incriminated in the development of bladder cancer in dogs.[2] In humans, occupational exposure from employment as aniline dyes manufacturers, painters, farmers, rubber workers, electrical workers, pesticide applicators, hairdressers, truck drivers, petroleum and other chemical industry workers have a well-established higher risk of bladder cancer.[2] Cigarette smoking, chronic cystitis, schistosomiasis of the bladder, and certain drugs (cyclophosphamide) are also believed to induce a higher risk of bladder tumors.[3]

Transitional cell carcinoma (TCC) is the most commonly diagnosed tumor in the urinary bladder of domestic animals. Approximately, 75-90% of primary epithelial urinary bladder neoplasms in dogs are TCC.[1] This is a neoplasm of older dogs (average 9-11 years) and apparently, females are more susceptible (2:1 ratio of female to male).[4,5] Breeds that may have a greater risk include Airedales, beagles, and Scottish terriers. Nearly 90% of affected dogs present with clinical problems referable to the urinary system such as hematuria, pollakiuria, or dysuria.[4] Paraneoplastic diseases associated with bladder tumors include hypercalcemia, cachexia, hyperestrogenism, hypertrophic osteopathy, and, as in this case, polycythemia.[1]

The most common location of TCC in dogs is in the trigone area of the urinary bladder. Most tumors are solitary and only rarely are multiple on gross examination. These tumors are divided based on their patterns of growth as papillary (project into the lumen), or nonpapillary (sessile or flat) and infiltrating (90% in dogs) or noninfiltrating (10% in dogs).[1]

Transitional cell carcinomas are one of the most malignant neoplasms in domestic animals. Metastases are present in the majority (50-90% of cases) of dogs at necropsy;[4,5] lungs and lymph nodes are the two most common sites, but bones[6] are frequently involved. In dogs, reported rates to regional lymph nodes are 48% and for distant sites 51%.[4,5] Some features have been associated with survival such as sex and treatment selection. Some investigators found that spayed females survive significantly longer than castrated males (358 days versus 132 days) and dogs that received doxorubicin or mitoxantrone in addition to a platinum based chemotherapeutic (either cisplatin or carboplatin) lived significantly longer than those that received only a platinum compound (358 days versus 132 days).[7]

This bitch was clinically normal one month after surgical removal of the mass. Unfortunately, the owner rejected the option of chemotherapy and there was not further clinical follow up.

AFIP Diagnosis: Urinary bladder: Transitional cell carcinoma, papillary and infiltrating, mixed-breed, canine.

Conference Comment: The contributor provides a thorough overview of transitional cell carcinoma, including etiology, location, and histomorphologic categorization. Conference attendees also discussed common causes of a positive urine occult blood test and how to differentiate hematuria from hemoglobinuria and myoglobinuria.

Hematuria is an increased erythrocyte concentration in the urine sediment and may be due to pathologic urinary system hemorrhage, iatrogenic hemorrhage, or genital tract hemorrhage. Causes of pathologic hemorrhage include the following: vascular damage due to trauma, inflammation, or renal infarcts; poor repair of small vessels due to thrombocytopenia, thrombocytopathia, or von Willebrand disease; or acquired or congenital coagulopathies. Iatrogenic hemorrhage may result from trauma during bladder palpation, cystocentesis, or catheterization. Genital tract hemorrhage is often associated with estrus in voided samples. Hemoglobinuria is most often due to intravascular hemolysis, while myoglobinuria is a result of muscle disease.[8]

With hematuria, the urine appears red and cloudy and will usually clear with centrifugation. Erythrocytes will be present in the urine sediment. There should not be clinical or laboratory evidence of hemolytic anemia or muscle disease. With hemoglobinuria, the urine is red to brown and does not clear with centrifugation and excessive numbers of erythrocytes will not be present in the sediment. There is a concomitant hemoglobinemia as free hemoglobin will discolor plasma before it saturates serum haptoglobin or causes hemoglobinuria. Clinically, there may be evidence of intravascular hemolytic anemia. With myoglobinuria, the urine is also red to brown, does not clear with centrifugation, and excessive numbers of erythrocytes will not be present in the sediment. Unlike hemoglobinemia, the plasma will be clear and of normal color. Clinical or laboratory evidence of muscle disease should be present rather than evidence of anemia. To differentiate urine hemoglobin from myoglobin in the laboratory, the addition of saturated ammonium sulfate solution will remove the color by precipitating the hemoglobin. Conversely, ammonium sulfate solution will not precipitate myoglobin and the urine will remain discolored. A better technique to differentiate hemoglobin from myoglobin is spectrophotometric analysis.[9]

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