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Department of Veterinary Pathology
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CONFERENCE 5
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CASE I - 5709 (AFIP 3028143).

Signalment: 4-year-old castrated male Romney Marsh sheep (*Ovis aries*).

History: A disease characterized by apathy, loss of weight and jaundice was observed in a herd of 200 Romney Marsh sheep, in a farm in southern Brazil. Twenty affected sheep died approximately 20 days after the first clinical signs. The flock was grazing a pasture severely infested by *Senecio brasiliensis* and *S. cisplatinus* which had evidence of being consumed by the sheep.

Gross Pathology: The sheep was emaciated and slightly icteric. The liver was enlarged and slightly yellowish (Fig. 1) and firm. The gallbladder was distended and the urine had a tan discoloration.

Histopathologic Description: Individual cell necrosis, loss of hepatocytes and vacuolar degeneration, hepatomegalocytosis, biliary ductal proliferation and periportal fibrosis were observed. Randomly, neutrophilic foci were also found. There was brownish pigment in macrophages and hepatocytes and intranuclear pseudoinclusions.

Contributor's Morphologic Diagnosis: Liver: Multifocal individual hepatocellular necrosis with loss of hepatocytes, vacuolar hepatocyte degeneration, periportal fibrosis, hepatomegalocytosis, intranuclear pseudoinclusions and bile duct hyperplasia, Romney Marsh sheep.

Contributor's Etiologic Diagnosis: Toxic hepatopathy

Etiology: *Senecio* spp. pyrrolizidine alkaloid toxicosis

Contributor's Comment: *Senecio* poisoning is one of the most important causes of death in cattle in Rio Grande do Sul, southern Brazil, causing 7% of all cattle deaths.[4] Sheep are more resistant than cattle to the toxicosis and frequently are used to control the plant.[1,5] Sheep required more than 2,0 of dried plant/kg of body weight to poison.[1]

The sheep resistance has been associated with the ruminal flora or to the capacity of the liver enzymes to detoxify pyrrolizidine alkaloids.[1] Different clinical pictures can be observed in the intoxication by pyrrolizidine alkaloids in sheep: (1) acute intoxication associated with the consumption of large amounts during a short time leading to liver necrosis; (2) primary chronic intoxication cause by the ingestion of large amounts of plant during long periods, causing diffuse hepatic fibrosis and megalocytosis; and (3) chronic copper intoxication associated with the storage of copper in the affected hepatocytes.[1]

Clinical signs in sheep include weight loss, photosensitization, nervous signs due to hepatic encephalopathy, and in cases of chronic copper poisoning jaundice and haemoglobinuria as a consequence of intravascular haemolysis.[1]

Outbreaks of poisoning by *Senecio* spp. in sheep are rare in Brazil. In Rio Grande do Sul only one outbreak has been reported previously, with some cases complicated by chronic copper intoxication.[2]

In the present outbreak, haemoglobinuria was not observed. Grazing for a long period of time in an area severely invaded by *Senecio* spp. caused primary chronic pyrrolizidine alkaloid intoxication. Nevertheless, the presence of brown yellowish pigment in hepatocytes and Kupffer cells suggests copper accumulation due to the hepatic lesion. Megalocytosis is characteristic of pyrrolizidine alkaloid intoxication. Other lesions are fibrosis and proliferation of bile duct cells. Pseudoinclusions result from the invagination of the plasmatic membrane, which stay sequestrated within the nucleus. Status spongiosus in the white matter of the brain was also observed in the sheep necropsied. This lesion is caused by different substances present in the blood of intoxicated animals, particularly ammonia.

AFIP Diagnosis: Liver: Hepatocellular degeneration and necrosis, multifocal, random, moderate, with marked megalocytosis, nodular regeneration, chronic portal hepatitis, and biliary hyperplasia, Romney Marsh sheep (*Ovis aries*), ovine.

Conference Comment: The contributor provides a concise summary of pyrrolizidine alkaloid toxicity in sheep. In addition to the key histomorphologic features of megalocytosis, periportal bridging fibrosis, biliary hyperplasia, and cytoplasmic

invaginations into the nucleus, conference attendees also observed oval cell hyperplasia and nodular regeneration.

Pyrrolizidine alkaloids have been found in various species of plants distributed worldwide. In addition to *Senecio*, the genera *Crotolaria*, *Heliotropium*, *Cynoglossum, Amsinckia*, *Echium*, and *Trichodesma* have also been known to cause disease.[6,7]

The most characteristic effect of toxic pyrroles is the induction of nuclear and cytoplasmic gigantism (megalocytosis). This effect is most likely due to an antimitotic effect with continued DNA synthesis as hepatocytes attempt to replace those that have undergone necrosis. Continued nucleoprotein synthesis, coupled with mitotic inhibition, probably accounts for the great increase in size of the nucleus and cytoplasm. The volume of megalocytic cells can range up to 20 times that of normal hepatocytes. Megalocytosis is not pathognomonic for pyrrolizidine alkaloid toxicosis. Other alkylating agents such as nitrosamine and aflatoxins can also result in megalocytosis. Concurrent with the development of megalocytosis, there is proliferation of the bile ducts and fibroplasia. This fibroplasia is generally minimal in sheep, moderate in horses and may be marked in cattle. Additionally, cytoplasmic invaginations into the nucleus are particularly common in chronic pyrrolizidine alkaloid toxicosis although they can occur in any chronically injured liver. Nodular regeneration can be present, but does not always occur due to the antimitotic effects of pyrrolizidines. However, during periods when animals are not grazing on pyrrolizidine alkaloid containing plants, hepatocyte replication can occur. Acidophilic spherical cytosegresomes are also a common finding.[6,7]

Acute poisoning by the pyrrolizidine alkaloids is uncommon due to unpalatability of the plants and results in periacinar necrosis and endothelial damage to the hepatic venules and small hepatic veins. This form of toxicosis is not clearly distinguishable from a variety of other hepatotoxins.[6]

In cattle, chronic pyrrolizidine alkaloidosis produces pronounced hepatic bridging portal fibrosis which infiltrates along the sinusoids to dissect lobules, separate individual cells, and link the walls of efferent veins. This form of fibrosis has been termed veno-occlusive disease.[6]

In sheep, long term consumption of pyrrolizidine containing plants may lead to elevated levels of liver copper followed by the hemolytic crisis of copper toxicity. In pigs, pyrrolizidine alkalosis primarily manifests as pneumonia and renal insufficiency. Pulmonary emphysema is a characteristic finding in pigs and horses. The pulmonary toxicity of pyrrolizidine alkaloids in rats is well recognized. The primary site of injury in this species appears to be the alveolar septa. The lesions

include severe vascular engorgement and edema, and diffuse fibrosis of alveolar and interlobular septa with patchy epithelialization.[6]
Type III or hepatogenous photosensitization may occur in association with pyrrolizidine alkaloid toxicosis secondary to hepatocellular damage and is due to the impaired capacity of the liver to excrete phylloerythrin, a break down product of chlorophyll. Phylloerythrin is carried to the dermis hematogenously where it is deposited and reacts with UV light forming reactive oxygen molecules, including free radicals. Mast cell degranulation and the production of inflammatory mediators cause damage to cell membranes, nucleic acids, proteins, and organelles. This is the most common type of photosensitization and occurs most frequently in herbivores. Lesions occur on areas of the body with nonpigmented skin and hair.[8]

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CASE II - C05-2714-1 (AFIP 3027385).

Signalment: 8-month-old, intact male, New Zealand White rabbit (*Oryctolagus cuniculus*).

History: Anesthesia had been induced with ketamine/acepromazine and the rabbit was being maintained on 2% isoflurane. During the intraoperative insertion of a large intramedullary nail filling the entire marrow cavity of the proximal half of the bilateral femora, the rabbit became cyanotic and died within 1 minute.

Gross Pathology: The trachea was slightly hyperemic and contained a small amount of foam. All lung lobes were mottled dark red (Figure C05-2714-G1), soft on palpation and floated in formalin. No other overt lesions were apparent.

Histopathologic Description: Throughout all sections of lung examined, numerous alveolar capillaries, pulmonary arterioles and arteries, and less frequently, venules and veins, contain intravascular lipid. The lipid appears as single to multiple, well demarcated, clear, round spaces that often displace circulating erythrocytes and leukocytes to the periphery of the vessel lumen and occasionally occlude vessel lumens. Also associated with the intravascular lipid are aggregates of hematopoietic precursors of the myeloid, erythroid and megakaryocytic series. Some alveolar spaces contain small amounts of eosinophilic proteinaceous material. Bronchial-associated lymphoid tissue is prominent. Fat emboli similar to those described above were also present multifocally in the choroid plexus of the brain and focally in the right ventricle of the heart (not submitted).

Contributor's Morphologic Diagnosis: Lung, pulmonary vascular fat embolism, acute, multifocal, marked.

Contributor's Comment: Fat embolism (FE), whereby fat released by marrow or adipose tissue enters the systemic circulation, occurs in virtually all cases of skeletal trauma such as long bone and pelvic fractures.[5,7,9,11,12] However, the clinical consequence of FE, known as fat embolism syndrome (FES) occurs in less than 10% of cases with an overall mortality rate of 5-15%.[5,7,9,11,12] FES is rare in children and the incidence increases with the number of fractures sustained by an individual.[12] Additional causes of FES include: mechanical disruption of adipocytes such as liposuction and hepatic lipidosis; mechanical disruption of bone marrow such as bone marrow harvest or transplantation; administration of exogenous fat

such as total parenteral nutrition or propofol infusion; and, miscellaneous conditions such as burns, acute sickle cell crises and pancreatitis.[5,9]

Regardless of the underlying cause, the pathogenesis of FES involves both mechanical obstruction and biochemical injury.[2,5-7,9,11,12] Fat from marrow is forced under pressure into torn venous sinusoids and mechanically obstructs capillaries in lungs, heart, kidneys, brain and skin. Activated platelets adhere to the surface of marrow fat, exacerbating vascular obstruction and tissue damage. If the amount of liberated fat and subsequent mechanical obstruction within the initial 12 hours after the injury is significant as in the case of this rabbit, fulminant FES characterized by pulmonary hypertension, right heart failure, shock and death ensues.[5,12] Interestingly, the acute lethal intravenous dose of fat in adult humans is 20-50 ml while the volume of femoral marrow fat is 70-100 ml.[5]

The amount of embolized fat often exceeds the fat content of bone. Furthermore, FES can occur in the absence of disrupted depot fat. Experimental *in vitro* and *in vivo* studies have demonstrated the agglutination of circulating chylomicrons and very low-density lipoproteins by C-reactive protein elevated during various infectious, inflammatory and neoplastic processes.[2,5,7,9,11,12]

Biochemical damage is ascribed to conversion of free fatty acids (FFAs) and glycerol from neutral fat and/or triglycerides by lipoprotein lipases which are activated by catecholamines elevated during stress. FFAs, particularly olein, are toxic to endothelial cells with subsequent disruption of vessel walls, vasogenic edema, perivascular bleeding, platelet aggregation and thrombosis. As an aside, the rare occurrence of FES in children is partially explained by FFA composition. Adult bone marrow has a higher fat content than the content of hematopoietic cells and contains more olein than palmitin and stearin while the opposite is true in the bone marrow of children.[12]

Patients are typically asymptomatic for 12-72 hours prior to presenting with the classical clinical triad of respiratory distress, cerebral dysfunction and a pathognomonic petechial rash on the neck, chest, axillae, conjunctiva and oral mucous membranes.[2,5-7,9,11,12] The latter is attributed to embolization of fat, which accumulates in the aortic arch, to nondependent skin via the subclavian and carotid arteries. The neurological manifestations vary widely from lethargy and confusion to seizures and paresis. Minor signs commonly seen include pyrexia, jaundice, retinal infarcts and oliguria or anuria. The delay in onset of clinical signs is attributed to the time required for conversion of neutral fat to FFAs. Consistent clinical pathology findings include unexplained anemia, thrombocytopenia and elevated serum lipase. FFAs bind to albumin and calcium resulting in hypoalbuminemia and hypocalcemia.

As there are no specific therapies for FES; prevention, early diagnosis and symptomatic treatment are crucial. First and foremost in instances of fractures is early immobilization. Surgical fixation typically involves external fixation and/or intramedullary nailing. However, intramedullary nailing as documented in this rabbit is also associated with FE due to marked increases in intramedullary pressure.[2,5,6,11,12] Venting holes distal to the fracture to promote drainage of the medullary cavity during insertion of the nail as well as bone-vacuum cementing techniques to prevent increases in intramedullary pressure have markedly reduced the incidence of FES.[5]

In veterinary medicine, documented cases of FE primarily involve surgical repair of long bone fractures in dogs and a cat or total hip arthroplasty in dogs.[4,11,13,15] FE restricted to glomerular tufts was reported in a diabetic dog following partial cystectomy for transitional cell carcinoma.[1] Reports in large animals are restricted to a 10-month-old Holstein-Friesian cow with Tetralogy of Fallot that died during surgery following costectomy to repair pulmonic stenosis.[14] Recently, FE has been described as a component of the "gas and fat embolic syndrome" found in beaked whales stranded subsequent to regional military sonar exposure.[3] Pulmonary FE was experimentally induced in rats with hepatic lipidosis and core body temperatures of 44°C.[8] This study was conducted to determine the contribution of hepatic lipidosis under elevated ambient temperatures to pulmonary FE. The authors had autopsied a middle-aged, homeless male found dead in a sauna who had pulmonary FE and hepatic lipidosis with no evidence of trauma.

Definitive confirmation of neutral lipids requires special histochemical staining of frozen sections with oil red O or sudan black B which was not performed in this case.

AFIP Diagnosis: Lung: Bone marrow and fibrocartilagenous emboli, numerous, New Zealand White rabbit (*Orytolagus cuniculus*), lagamorph.

Conference Comment: The contributor provides an excellent summary of fat embolism syndrome. Embolism is defined as the occlusion of arteries by lodgement of foreign materials.[16] Types of emboli other than fat emboli include thromboemboli, fibrocartilagenous emboli, bacterial emboli, fungal emboli, parasitic emboli, and neoplastic emboli. Less common sources of emboli include hematopoietic cells from bone marrow, amniotic fluid, agglutinated erythrocytes, or clumps of other cells released after tissue trauma. The significance in all cases, is the potential of emboli to occlude vessels and inhibit blood flow to dependent tissues.[16-20]

The lungs act as a "safety net" that catch emboli before they can reach the brain and other tissues. The most common pulmonary emboli in domestic animals include thromboemboli, septic (bacterial) emboli, fat emboli, and neoplastic emboli. Infarction due to pulmonary emboli is rare due to the lung's dual arterial circulation (pulmonary and bronchial arteries).[18]

Pulmonary thromboemboli typically originate from a thrombus located elsewhere in the venous circulation. Fragments released eventually reach the lungs and lodge in the pulmonary vasculature. Small sterile thromboemboli are clinically and pathologically insignificant due to rapid degradation by the fibrinolytic system. In the dog, causes of pulmonary arterial thrombosis and subsequent pulmonary thromboembolism include *Dirofilaria immitis*, *Angiostrongylus vasorum*, hyperadrenocorticism, hypothyroidism, and hypercoagulable states. Additionally, long-term intravenous catheterization can cause thrombosis of the jugular vein from which fragments can break resulting in pulmonary thromboembolism.[18]

Septic emboli containing bacterial or fungal fragments most often originate from bacterial endocarditis (tricuspid valve) and jugular thrombophlebitis in all species; hepatic abscesses that have eroded into the caudal vena cava in cattle; and septic arthritis and omphalitis in farm animals. Large numbers of septic emboli may result in sudden death due to massive pulmonary edema. Survivors typically develop embolic, suppurative pneumonia that may progress to pulmonary abscesses in addition to pulmonary arteritis and thrombosis.[18]

As pointed out by the contributor, fat emboli can form following bone fractures or surgical/clinical interventions of bone. These are not as significant of a problem in domestic animals as they are in humans.[18]

Pulmonary neoplastic emboli can be numerous and the ultimate cause of death in malignant neoplasia. Hepatic emboli occasionally lodge in the pulmonary vasculature following severe trauma and hepatic rupture. Interestingly, pulmonary vascular brain emboli, reported in cases of severe head injury in humans, have been reported in cattle following pneumatic stunning at slaughter. Although brain emboli are not an important antemortem pulmonary lesion, they may pose a potential public health risk in bovine spongiform encephalopathy (BSE).[18]

Trophoblastic emboli have been reported in the chinchilla.[21] In species with hemochorial placentation (humans, nonhuman primates, rabbits, and rodents), fetal trophoblastic cells are in direct contact with maternal circulation. Trophoblasts erode through the endometrium, migrate into the lumina of maternal blood vessels, through the uterine vessels, and into the mesovarium and mesometrial vessels. Trophoblasts can subsequently dislodge and are carried to small capillary beds such

as in the lungs. Domestic animals without hemochorial placentation are not prone to trophoblastic emboli.

Contributor:
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CASE III - 97733 (AFIP 2890214).

Signalment: 2-year-old, male, F344 rat, *Rattus norvegicus*.

History: Tissue from a rat used in a two year chronic toxicology study.

Gross Pathology: There was generalized lymphadenomegaly and splenomegaly (10x normal size). The liver had a granular appearance. The right kidney was deformed and the opposite renal cortex was mottled. There was generalized pallor and mild icterus.

Histopathologic Description: The spleen is markedly enlarged and white pulp is sparse or absent. Erythrocytes and neoplastic round cells distend the sinusoids. The neoplastic cells have scant amounts of granular (faintly) cytoplasm and round, oval or cleaved open-faced nuclei. Cell margins are irregular but distinct. Most high power fields contain one or two mitotic figures. A few foci of extramedullary hematopoiesis are evident in some sections.

Liver sinusoids and blood vessels are partially filled with the previously mentioned neoplastic cells. In addition, several larger vessels contain cellular emboli. The emboli are composed predominately of a second population of round to spindloid cells with distinct to indistinct cytoplasmic borders, a moderate amount of pale pink cytoplasm and round to elongate open-faced nuclei. Multinucleate giant cells (few) and karyomegaly are evident in some sections. There is moderate to severe bile duct hyperplasia. Minimal to mild oval cell hyperplasia is present in some sections. Randomly distributed throughout the liver, but more prominent in centrilobular areas, are large macrophages and giant cells distended with vacuoles, small acicular clefts, and variable amounts of light brown pigment. Frequently, hepatic parenchyma is replaced by the inflammatory infiltrate.

Contributor's Morphologic Diagnoses: 1. Spleen: Leukemia, Mononuclear Cell.
2. Liver: Leukemia, Mononuclear Cell.
3. Liver: Histiocytic sarcoma, metastatic.
4. Liver: Inflammation, granulomatous, multifocal, moderate.
5. Liver, bile duct: Hyperplasia, severe.

Contributor's Comment: Mononuclear cell leukemia is also referred to as Fischer rat leukemia and large granular lymphocytic leukemia. The term mononuclear cell leukemia is used in NTP studies to maintain consistency and avoid confusion. Mononuclear cell leukemia is common in aged Fischer 344 rats. Immune-mediated hemolytic anemia is commonly seen in affected rats. Occasional neoplastic cells contain phagocytized erythrocytes. The neoplastic cells are of uncertain linage but are known to have characteristics of T cells and macrophages. Ultrastructural studies have revealed the cytoplasmic granules to be densely osmophilic membrane-bound lysozomes. The cells stain for napthol AS-D acetate esterase, beta-glucuronidase and acid phosphatase and are positive for OX-8 by immunocytochemistry. Current theory is that the neoplastic cells are effector cells for NK cell activity in the rat. A low incidence of mononuclear cell leukemia (large granular lymphocyte leukemia) has been reported in Wistar-Furth, Wistar and Sprague-Dawley strains.

Histiocytic sarcoma is relatively common in Sprague-Dawley derived strains but has a low incidence in Fischer, Wistar and Osborne-Mendel rats. In F344 and Sprague-Dawley strains, the liver and lungs are the most commonly and extensively affected organs, however the subcutis is more commonly the primary site of involvement in the Wistar rat. These tumors are frequently associated with hyaline droplet accumulation in the P2 segment of renal proximal convoluted tubules. The hyaline droplets are positive for lysozyme and negative for alpha-2 mu globulin. Tumor cells are positive for lysozyme, alpha-1 trypsin and alpha-1 chymotrypsin by immunocytochemistry.

Foci of granulomatous inflammation are incidental findings in aging rats. Incidence and severity is variable but generally more prevalent in females than males.

AFIP Diagnoses: 1. Liver, spleen: Large granular lymphocytic leukemia, F344 rat (*Rattus norvegicus*), rodent.
2. Liver, veins: Histiocytic sarcoma.
3. Liver: Hepatocellular degeneration and necrosis, multifocal, random, mild, with biliary hyperplasia.
4. Spleen, white pulp: Lymphoid depletion.

Conference Comment: Large granular lymphocytic leukemia (LGL) is a common cause of death in aging F344 rats and occasionally occurs in other strains (Wistar, Wistar-Furth). LGL appears to arise in the spleen and then spreads to other organs such as the lymph nodes, liver, and lungs.[8] Previous studies have shown that splenectomy markedly reduces the incidence of LGL.[2,3]

Typical clinical pathology findings include a marked leukocytosis with leukocyte counts of up to 400,000/ml^3, immune-mediated hemolytic anemia, thrombocytopenia (immune-mediated, DIC), clotting abnormalities, increased conjugated and unconjugated bilirubin, bilirubinuria, urobilinogenuria, hemoglobinuria, and increased liver enzymes.[2,8]

The most consistent gross finding is splenomegaly. Additionally, there may be moderate to marked hepatomegaly with an accentuated lobular pattern. Lymphadenopathy, icterus, and petechial hemorrhages on the lung and lymph nodes may also occur.[2,3,8]

Key histopathologic features include diffuse infiltration of the spleen, lymph nodes, liver, and lungs with malignant lymphocytes. There is marked depletion of splenic lymphoid follicles and diffuse infiltration of leukemic cells in hepatic sinusoids. Centrilobular hepatic degeneration commonly occurs secondary to anemia and neoplastic infiltrates. Erythrophagocytosis occurs in the liver and spleen.[2,3,8]

The fine cellular details of the large granular lymphocytes are not visible in fixed tissue sections, but can be seen in peripheral blood smears or stained impression smears of tissues such as the spleen and include 10-15 um diameter lymphocytes with round to oval, irregular or reniform nuclei; pale cytoplasm; and prominent azurophilic granules. Ultrastructurally, the azurophilic granules appear as electron dense membrane-bound lysosomes. The ultimate cause of death is often attributed to immune mediated hemolytic anemia and centrilobular hepatic degeneration.[2,3,8]

Histiocytic sarcomas most commonly occur in aging Sprague-Dawley rats, but also occur in other strains (Osborne-Mendel, Wistar, Fischer). Grossly, the neoplasm is pale tan and firm and can appear as irregular masses or infiltrate and displace normal tissue in the liver, lymph nodes, lungs, spleen, mediastinum, retroperitoneum, and the subcutis. Histologically, histiocytic sarcomas appear as sheets of elongate palisading fusiform cells to pleomorphic histiocytic cells with abundant cytoplasm that may contain vacuoles or phagocytized erythrocytes. Nuclei are vesiculate with prominent nucleoli. Multinucleated giant cells of the Langhans type are commonly present in tumors with a prominent histiocytic component. Areas of necrosis surrounded by palisading tumor cells are common and characteristic of histiocytic sarcoma. Fibrosis varies from minimal to marked.[7,8]

Contributor: Experimental Pathology Laboratories, Inc.

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CASE IV - 06-1714 (AFIP 3026011).

Signalment: 10-month-old, male, Boxer, canine.

History: This 10-month-old Boxer had a three to five day history of neck pain and stiff gait. There were no neurological deficits noted at that time. The dog underwent general anesthesia for cerebrospinal fluid collection. The dog recovered, but one hour after extubation it collapsed. There was no pulse or heart beat. Resuscitative attempts were unsuccessful.

Gross Pathology: The brain and spinal cord were removed by the referring veterinarian. He noted diffuse, subdural hemorrhage around the cervical spinal cord.

Laboratory Results: The spinal fluid had 5,310 white blood cells and 8,370 erythrocytes per milliliter. The protein was 260 mg/dl. Cytologically, there was a neutrophilic pleocytosis and no etiologic agents were observed.

Aerobic culture of the meninges was negative for bacterial growth.

Histopathologic Description: The sections of cervical spinal cord have several small to medium-sized muscular arteries in the leptomeninges with infiltrations of the tunica adventitia, tunica muscularis and tunica intima by neutrophils and a few macrophages. There is deposition of homogenous eosinophilic material and karyorrhectic debris (fibrinoid necrosis) within the tunica media of some affected vessels. There are diffuse infiltrates of neutrophils and fewer macrophages within the surrounding leptomeninges. There is diffuse hemorrhage in the subdural space.

Contributor's Morphologic Diagnoses: 1. Vasculitis, acute to subacute, multifocal, severe with fibrinoid necrosis, severe, meninges, cervical spinal cord.
2. Subdural hemorrhage, acute, diffuse, severe, cervical spinal cord.

Contributor's Comment: The signalment, clinical signs and lesions are consistent with the idiopathic condition known as juvenile polyarteritis syndrome or "beagle pain syndrome." The term beagle pain syndrome was used in the first descriptions of the disease as it was observed in young laboratory beagle dogs that were part of chronic toxicity studies.[1,2] It has subsequently been seen in other breeds.[3]

Young dogs, typically 4-10 months-of-age, are affected. Clinical signs are characterized by acute onset of fever, anorexia and cervical pain. Affected dogs assume a hunched stance and have a reluctance to move. Signs tend to wax and wane.[4] Cerebrospinal fluid analysis reveals moderate to severe neutrophilic pleocytosis and elevations in protein. There is typically a peripheral neutrophilia.[4]

Thus far, no etiologic agents have been identified in affected dogs. Since the disease responds to corticosteroid therapy, an immune-mediated etiology is suspected.[4]

The histologic lesions are those of vasculitis that may involve multiple organs but are seen most consistently in vessels of the cervical spinal cord, mediastinum and heart.[4] Thrombosis and loss of vascular integrity with hemorrhage may be present.[3,4] Presumably, acute subdural hemorrhage with compression of vital portions of the cranial cervical cord was responsible for the acute collapse and death of this dog. Some sections of cranial cervical cord (not submitted) contained evidence of swollen axons in white matter funiculi.

Similarities in clinical signs suggest that the juvenile polyarteritis syndrome and the clinical entity known as steroid responsive suppurative meningitis are related diseases. However, since the latter responds well to corticosteroids there are no good histological studies to confirm this relationship.[3,5] The present case had a clinical diagnosis of steroid responsive suppurative meningitis based on the clinical findings. The histologic lesions presented here are characteristic for the juvenile polyarteritis syndrome and suggest that the two diseases may indeed be the same.

AFIP Diagnosis: Spinal cord and meninges: Vasculitis, necrotizing, multifocal, marked, with neutrophilic and histiocytic meningitis and severe meningeal hemorrhage, Boxer, canine.

Conference Comment: The contributor provides a concise summary of canine juvenile polyarteritis syndrome or "beagle pain syndrome." The severity of the vasculitis varied between slides. Additionally, some sections of cervical spinal cord contained multifocal neutrophilic and histiocytic peridural steatitis and polyradiculoneuritis.

Lesions similar to canine juvenile polyarteritis syndrome are seen in aging rats with polyarteritis nodosa. This spontaneous disease occurs most commonly in male Sprague-Dawley rats, spontaneous hypertensive rat strains, and rats with late-stage chronic nephropathy. Arterial lesions most commonly occur in the mesentery, pancreas, pancreaticoduodenal artery, and testis. However, lesions may be seen in various other organs except the lung. Histologically, there is fibrinoid degeneration and thickening of the media of affected arteries with neutrophilic and monocytic infiltrates. Lumina of affected vessels vary in size and contour. Thrombosis with recanalization can occur. An immune-mediated pathogenesis is suspected, but has not been confirmed.[6]

Polyarteritis nodosa occasionally occurs in cattle and other domestic species.[7]

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