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Department of Veterinary Pathology  
WEDNESDAY SLIDE CONFERENCE  
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CONFERENCE 19  
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CASE I – 3006 (AFIP 2787431)

**Signalment:** 10-months-old, male, Fischer 344 rat

**History:** This rat was in a study utilizing a surgically induced model of chronic renal failure.

**Gross Pathology:** At necropsy, multiple, tan, raised nodules (<0.5 cm) were noted along the serosal surface of the epididymides, intra-abdominal adipose tissue, and the body wall. Other gross findings were directly related to the surgical model and/or were secondary to renal failure.

**Laboratory Results:** Clinical pathology findings (markedly elevated BUN and creatinine, decreased total protein and albumin, and alterations in electrolytes) were consistent with renal failure, as expected.

**Contributor's Morphologic Diagnosis:** Skeletal muscle, adipose and serosa (Body wall); mesothelioma

**Contributor's Comment:** Mesotheliomas are one of the most common neoplasms in the F344 rat. In the F344 rat, spontaneous mesotheliomas are believed to arise from the tunica vaginalis. Most early neoplasms are therefore found adherent to the epididymis or tunica albuginea. The location of the nodules along the epididymides and adjacent adipose and body wall in this rat is consistent with this observation. The papillary appearance and prominent stroma of the submitted neoplasm are typical of this neoplasm in the F344 rat. Many sections also had infiltration of the neoplasm by variable numbers of mast cells, eosinophils, lymphocytes, and macrophages containing intracellular, coarse, brown pigment (hemosiderin). These cellular infiltrates are also common features of this neoplasm.

**AFIP Diagnosis:** Body wall: Mesothelioma, Fischer 344 rat, rodent.

**Conference Comment:** Mesotheliomas occur on pleural, pericardial, and peritoneal surfaces; can be associated with effusions; and are all considered malignant. Spread is usually by direct transplantation of neoplastic cells rather than by lymphatic/hematogenous routes or direct invasion. Most mesotheliomas are papillary, and consist of variable layers of mesothelial cells covering pedunculated fibrovascular stalks. The predominant cell type, mesothelial or stromal, may vary, more closely resembling a carcinoma or fibrosarcoma, respectively.

Histochemically, staining with PAS and Alcian blue demonstrates mucopolysaccharides within the cytoplasm of neoplastic cells. Pretreatment with hyaluronidase eliminates positive staining supporting hyaluronic acid as the predominant mucopolysaccharide. By immunohistochemistry, neoplastic cells may be positive for keratin and vimentin.

The primary differential diagnosis discussed in conference was mesothelial hyperplasia. The appearance of individual hyperplastic cells may not differ greatly from those in neoplastic lesions. Hyperplastic lesions are defined as focal thickenings or single papillary projections of mesothelial cells without stromal proliferation.

**Contributor:** Lilly Research Laboratories, Greenfield, IN 46140

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**CASE II – 01N-1471 (AFIP 2788702)**

**Signalment:** 4-year-old, female, Saanen, Caprine.

**History:** This doe has an 11-month history of coughing and mild lethargy, and a 5-month history of swollen carpal joints. She was diagnosed with pneumonia and treated with antibiotics (Naxcel) and vitamin B, which were unsuccessful. She was current on vaccinations and had been recently dewormed. The doe developed a left head tilt that quickly progressed to circling to the left. The neurologic signs lasted two weeks and on the day before euthanasia the doe was depressed, had decreased conscious proprioception (bilaterally symmetrical) and nystagmus.

**Gross Pathology:** On necropsy the doe was in good nutritional condition and weighed 29kg. The lungs failed to collapse, were diffusely firm and heavy, and the

caudal lobes were more severely affected. The cut surface of the lungs was mottled tan to brown-red and often had a tan nodular pattern. Both carpi were swollen and expanded dorsally by pockets of tan connective tissue that did not appear to communicate with the joint space. Within the connective tissue pocket of the right carpal joint there was a collection of abundant viscous clear fluid admixed with flocculent tan material (pus). There were multiple dark red to gray speckles throughout the thalamic region and the meningeal blood vessels were congested.

**Laboratory Results:** The lung cultures were negative for *Mycoplasma* sp. The joint fluid was cultured for *Mycoplasma* sp., and aerobic and anaerobic bacteria with negative results.

Immunohistochemistry for CAE was performed in formalin tissue sections from brain and lungs.

**Contributor's Morphologic Diagnoses:**

1. Lungs: Severe, chronic, diffuse, lymphoplasmacytic interstitial pneumonia with extensive fibrosis, type II pneumocyte hyperplasia and marked alveolar proteinosis and histiocytosis (Caprine Arthritis Encephalitis Virus).
2. Brain (right thalamus) (Not submitted): Severe, multifocally extensive, chronic, lymphoplasmacytic and histiocytic encephalitis with central malacia, and multiple glial nodules (Caprine Arthritis Encephalitis Virus).
3. Carpal joints, bilaterally (Not submitted): Moderate, diffuse, chronic, lymphoplasmacytic and proliferative arthritis and tenosynovitis with focal hygroma formation (Caprine Arthritis Encephalitis Virus).

**Contributor's Comment:** Caprine Arthritis Encephalitis virus is a lentivirus from the family *Retroviridae* that causes persistent infections in goats. It is closely related to Maedi-Visna virus, the agent of Ovine Progressive Pneumonia (OPP). These lentiviruses are genetically related to Equine Infectious Anemia virus and the immunodeficiency viruses of humans and animals. The CAE syndrome was first described as a leukoencephalomyelitis of young goats, and CAEV was first isolated from synovial membrane of adult goats with arthritis. Both OPP and CAEV persist in the infected sheep and goat respectively within macrophages and monocytes and cause arthritis, encephalitis, mastitis and pneumonia.

The progression of the disease is insidious and therefore clinical signs and lesions are usually seen in adult animals. The virus-infected macrophages induce lymphocytes to produce large amounts of non-neutralizing antibodies, primarily against the viral core protein. These large immunocomplexes are thought to play an important role in the pathogenesis of the chronic lesions seen in OPPV and CAEV infections.

Pneumonia is the principal manifestation of OPP and an infrequent clinical presentation in CAE. Chronic polyarthritis is the main clinical outcome of CAEV infection in adult goats. The carpal joints are almost always affected and grossly swollen. Variable degrees of chronic lymphoplasmacytic arthritis are detected histologically in multiple other joints. The transmission of these viruses occurs mainly through colostrum and milk from the infected ewe or doe to the offspring. Intrauterine transmission has been reported to occur rarely for OPPV. Direct contact among adults, except during lactation or overcrowded situations, may result in transmission, but is not a significant route.

The pulmonary lesions caused by OPPV and CAEV have a similar gross and histologic appearance and consist mainly of a non-suppurative interstitial pneumonia with type II pneumocyte hyperplasia and lymphoplasmacytic and histiocytic infiltration of septa and of perivascular, peribronchial and peribronchiolar spaces. Lymphoid follicles with germinal centers are often found scattered in these locations.

A unique feature of the pneumonia induced by CAEV is the prominent alveolar proteinosis, which is not seen in OPP and is rarely encountered in animals, with the exception of rats and mice. This case demonstrates the classic histologic picture of CAEV induced pneumonia with alveolar proteinosis. This animal also had concomitant encephalitis and arthritis. CAEV encephalitis is usually seen in young goats (2-4 months). However, infected adult goats with polyarthritis frequently present some degree of encephalitis, mastitis and pneumonia. Other lesions in both OPPV and CAEV infections are a lymphoplasmacytic perivascular leukoencephalomalacia and demyelination, lymphocytic arthritis and mastitis.

Highly specific and sensitive enzyme-linked immunosorbent assays (ELISA) are currently available for the serologic diagnosis of ovine lentivirus infections in sheep and goats. The ELISA detects antibodies against a major core protein of the OPP virus and cross-reacts with CAEV.

Serology was not performed in this particular animal but immunohistochemistry, classic clinical signs and pathologic lesions confirm this didactic case of CAEV infection.

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**AFIP Diagnosis:** Lung: Pneumonia, interstitial, lymphocytic, chronic, diffuse, severe, with abundant intraalveolar eosinophilic proteinaceous material and mucin, Saanen goat, caprine.

**Conference Comment:** The contributor has provided a concise review of this entity.

**Contributor:** University of California, Davis, Veterinary Medical Teaching Hospital,

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2. Knowles D: Laboratory Diagnostic tests for retrovirus infections of small ruminants. *Vet Clin North Am (Food Animal Practice)* **13**:1-11, 1997
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**CASE III – OL8546 (AFIP 2796586)**

**Signalment:** 8-month-old, male, Beagle, dog

**History:** Eight weeks after the start of a toxicology study, a male dog from the control group suddenly developed a bilateral swelling of the head. This clinical sign was associated with moderate fever (103.3 F), discomfort, slight unilateral prolapse of the third eyelid, and profound pain when the head was touched. The dog could barely open his mouth to drink and was completely anorexic. During clinical examination, the dog had difficulty opening its mouth (trismus). The swelling appeared to be located mostly on the caudal side of the right temporal muscle. In addition, submandibular lymph nodes were enlarged bilaterally.

**Gross Pathology:** Both temporal muscles were swollen with large areas of hemorrhagic necrosis. Submandibular lymph nodes were enlarged with areas of hemorrhages.

**Laboratory Results:** Detailed serum chemistry and hematological examinations were performed. There were no hematological abnormalities. However, several serum chemistry parameters were increased compared with our historical values for beagle dogs of this age.

<b>Chemistry Parameters (units)</b>	<b>Values</b>	<b>Historical Range (Mean +/- Standard Deviation)</b>
Aspartate Aminotransferase (U/L)	195	30 ± 5.2
Creatine Kinase (U/L)	3598	150 ± 52

Alanine Aminotransferase (U/L)	92	41 ± 7.3
Alkaline Phosphatase (U/L)	153	93 ± 17.7
Globulin (g/dL)	3	2.2 ± 0.26
Cholesterol (mg/dL)	202	141 ± 22.4

**Contributor's Morphologic Diagnosis:** Marked, diffuse, chronic active plasmacytic temporal myositis with acute hemorrhagic necrosis

Condition: Masticatory Muscle Myositis (Acute Form)

**Contributor's Comment:** Throughout both temporal muscles, there are large coalescing areas of acute and subacute hemorrhagic necrosis characterized by hyaline, floccular and granular degeneration of myofibers with multifocal mineralization, and accumulation of red blood cells, fibrin, and cellular debris. Around and within these areas of necrosis, there are infiltrates of mostly macrophages with multifocal accumulation of neutrophils and multifocal proliferation of fibroblasts embedded in a loose, immature, edematous and myxomatous fibrous tissue. Multifocally, there are frequent perivascular and interstitial, small to large infiltrates of mostly plasma cells with fewer lymphocytes and rare eosinophils and neutrophils. In addition, there are frequent areas of myofiber regeneration characterized by central nuclei and myotube cells.

Masticatory muscle myositis (MMM) is a canine inflammatory disorder selectively involving the muscles of mastication (masseter, temporal and pterygoid muscles). It is presently thought that this disorder is caused by an immune reaction directed toward masticatory muscles, which are composed primarily of a unique type 2M myofiber. These type 2M myofibers are considered central to the pathogenesis of this disorder; since affected dogs have circulating autoantibodies directed toward their unique myosin component. The type of inflammatory infiltrate (predominantly lymphocytes and plasma cells), as well as the clinical response to immunosuppressive doses of corticosteroids, supports an immune-mediated mechanism. MMM can occur in any breed of dogs, young and middle-aged dogs are primarily affected and there is no gender predilection. MMM can be recognized in an acute form (also known as eosinophilic myositis) or a chronic form (also known as atrophic myositis). In the acute form, there is recurrent painful swelling of the masticatory muscles with possible exophthalmos, prolapse of the third eyelid, blindness, pyrexia, trismus, swelling of local lymph nodes, anorexia, or salivation. These episodes may last from 1 to 3 weeks. In contrast, the hallmark of the chronic form is a progressive atrophy of the masticatory muscles without systemic signs, resulting in a skull-like appearance of the head. The chronic form is by far the most commonly recognized form of this disorder. The diagnosis is based on clinical and laboratory findings. In the acute form, because of the on-going

widespread muscle necrosis, there is usually an elevation of serum creatine kinase (CK), aspartate aminotransferase (AST), and globulins. A definitive diagnosis can be obtained by demonstrating circulating autoantibodies against type 2M fibers. Because of the suspected immune-mediated basis, treatment involves the administration of immunosuppressive doses of corticosteroids or other immunosuppressive drugs like azothioprine. Long-term or lifelong therapy may be required.

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**AFIP Diagnosis:** Skeletal muscle: Myositis, necrotizing, chronic-active and eosinophilic, diffuse, moderate, Beagle, canine.

**Conference Comment:** The differential diagnosis for masticatory muscle myositis (MMM) includes canine idiopathic polymyositis (PM) and familial canine dermatomyositis (DM).

PM usually affects large breed adult dogs. These animals present with focal, multifocal, or generalized muscle atrophy and weakness with pain on palpation. Dysphagia, dyspnea, and megaesophagus can follow involvement of the muscles of mastication, respiration, or deglutition. CK, AST, and ALT are variably elevated. The pathogenesis is thought to be immune mediated as IgG antibodies have been demonstrated bound to the sarcolemma of affected muscle fibers. Histologically, lymphoplasmacytic, histiocytic, and neutrophilic inflammation surrounds degenerate and necrotic type I and type II muscle fibers.

DM is a disease of young Collies, Shetland Sheepdogs, and their crosses and has an autosomal dominant mode of inheritance. Pathogenesis is suspected to involve immune complex deposition; the antigen is unknown. Muscle weakness and atrophy follows cutaneous lesions (pustules, vesicles, erosions, and crusts) that first appear on the face, around the ears, and over bony prominences. The myositis, which is often in direct proportion to the dermatitis, may reflect extension of inflammation from the overlying skin. Like MMM and PM, atrophy of the temporalis and masseter muscles can lead to dysphagia. Elevations in CK are often minimal. Histologically, the myositis is characterized by lymphoplasmacytic, histiocytic, neutrophilic, and eosinophilic infiltrates. There is degeneration, atrophy, and necrosis of striated muscle with eventual fibrosis. A fibrinoid vasculitis is often present in both the muscle and skin. The cutaneous lesion, which bears similarity to SLE, is characterized by basal cell apoptosis (Civatte bodies), dermo-epidermal vesicles, follicular atrophy, and perifollicular and perivascular inflammation. While neither lesion is individually distinctive, the diagnosis is based on breed association supported by typical clinical, gross, and histological findings.

**Contributor:** Pharmacia Corporation, Pathology Laboratory, Skokie, IL 60077

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#### **CASE IV – HN1708 (AFIP 2789968)**

**Signalment:** Ten-month-old, male, Shiba, dog

**History:** The affected dogs showed progressive clinical signs of predominantly cerebellar ataxia and resting and intentional type of head tremor from approximately six months of age. After that clinical signs included hypermetria, tetraplegia, ataxia abasia, and generalized muscle rigospasticity were also prominent.

**Gross Pathology:** Grossly, marked cerebral atrophy with yellow discoloration was observed. The width of cerebral white matter was decreased.

**Laboratory Results:** Vacuolated lymphocytes suggesting a storage disorder were seen in the peripheral blood and activity of B-galactosidase in leukocytes at one month of age (1.33 nmol/hr/mg protein) was approximately 1% of those of control dogs (130 nmol/hr/mg protein, n = 13). High performance thin-layer chromatographic analysis demonstrated an abnormal accumulation of GM1 ganglioside (27.1 nmol N-acetylneuraminic acid (NANA)/mg protein) in the brain at ten months of age. A five month old male beagle for control revealed 2.07 nmol NANA/mg protein of cerebral GM1 ganglioside.

**Contributor's Morphologic Diagnosis:** Cerebrum and cerebellum: distention and loss of neurons due to cytoplasmic accumulation of storage materials, mild to severe, diffuse, Shiba dog, canine.

**Contributor's Comment:** GM1 gangliosidosis is a lysosomal storage disease caused by deficient activity of lysosomal acid B-galactosidase. The genetic disorder is



generally inherited as an autosomal recessive trait. Previously, GM1 gangliosidosis has been identified and studied in humans, cats, cattle, dogs, and sheep. The canine form has been described in English Springer Spaniels (ESS), Portuguese Water Dogs (PWD), mixed-breed Beagles, Alaskan Huskies (AH), and Shiba dogs. This case has a genetic relationship to the Shiba dogs with GM1 gangliosidosis in the previous report.

Microscopic examination revealed severe distention and loss of neurons with diffuse microgliosis and diffuse astrocytosis throughout the central nervous system. Neuronal loss was noted especially in the Purkinje cell layer in the cerebellum. Vacuolated macrophages and rod-shaped microglia were diffusely scattered in both the gray matter and white matter. The cytoplasmic vacuoles of diffusely scattered macrophages were clear and occasionally contained a small amount of filamentous substance. Luxol fast blue stain and immunohistochemistry for MBP showed decreased number of mature oligodendrocytes and reduced expression of MBP in the white matter, suggesting hypomyelination or dysmyelination.

These pathologic findings were all mostly similar to those of GM1 gangliosidosis in other dog breeds. Ultrastructurally, typical membranous cytoplasmic bodies (MCB) were observed in Purkinje cells and small granular cells. Neuronal storage materials were negative to weakly positive for lipid staining, PAS-positive, positive for anti-asialo GM1 antibody in frozen sections, and stained with lectins, including Con A, DBA, SBA, and RCA-1 in paraffin-embedded sections. The results of lectin staining suggest that the storage materials contain different substances from those of the canine GM1 gangliosidoses in ESS and PWD.

Dysmyelination was reported in GM1 gangliosidosis of ESS and PWD as well as the disease of other species. Recently, a significant loss of oligodendrocytes was demonstrated in the gray matter and white matter of affected AH by detecting proteolipid protein (PLP) mRNA in oligodendrocytes using in-situ hybridization. The findings suggested hypomyelination.

The features of the vacuoles in macrophages apparently differ from the storage materials in affected neurons. Such a response has not been emphasized in the previous canine forms of this disease. The cytoplasmic materials of macrophages were stained with Con A, RCA-1, and WGA in paraffin-embedded sections and the reactivities slightly differ from those of intracytoplasmic storage materials of neurons. It was unclear whether the vacuolated macrophages merely play the role of scavenger cells, engulf the released materials from ruptured neurons with cell debris and accumulate within the CNS, or they are other essential morphology associated with GM1 gangliosidosis.

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**AFIP Diagnosis:** Cerebrum and cerebellum, neurons and glial cells: Cell swelling and intracellular foamy/granular material, diffuse, moderate, with neuronal loss, Shiba, canine.

**Conference Comment:** Gangliosidoses are lysosomal storage diseases that fall under the broader category of sphingolipidoses. Sphingolipids are structural lipids and specific modifications of the ceramide component results in gangliosides, globosides, or sphingomyelin. Sphingolipidoses include GM1 and GM2 gangliosidosis, globoid cell leukodystrophy (Krabbe disease), metachromatic leukodystrophy, Glucocerebrosidosis (Gaucher's disease), and sphingomyelin lipidosis (Niemann-Pick disease). Additional species in which GM1 gangliosidosis has been described includes Friesian cattle, Coopworth-Romney sheep, and Suffolk sheep.

GM2 Gangliosidosis is characterized by a defect in hexosaminidase, which exists in two forms Hexosaminidase A and B. Hexosaminidase A consists of one alpha and one beta subunit; Hexosaminidase B, two beta subunits. The specific subunit defect varies by species; in German Shorthair Pointers and domestic shorthair cats it is a beta subunit defect. In humans, mutations in the alpha subunit result in hexosaminidase A deficiency (Tay-Sachs disease). Mutations in the beta subunit result in deficiencies in both Hexosaminidase A and B (Sandhoff disease).

**Contributor:** Laboratory of Comparative Pathology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan

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