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Department of Veterinary Pathology
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Conference Moderator:
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CASE I: 04-0556-7 (AFIP 2936145).

Signalment: Two-year-old, male, Rottweiler dog, canine (*Canis familiaris*).

History: This dog was presented with a two month clinical history of slowly progressive and relentless ataxia, hypermetria and proprioceptive loss of forelimbs with final paresis. Cranial nerve function and spinal reflexes appeared normal. No pathological nystagmus or tremors were observed. The dog was euthanized. Parents of this dog were apparently normal.

Gross Pathology: At necropsy no organic gross lesions were observed other than a white, more or less bilateral, opaque discoloration of the dorsolateral funiculus of spinal cord.

Laboratory Results: Myelography of cervical spinal cord revealed no compression lesion.
Magnetic resonance imaging (MRI) of the cervical spinal cord and brain was normal.
Cerebrospinal fluid (CSF) cytology revealed a normal protein content of 0.30 g/L (normal=0-0.45 g/L) and no pleocytosis.

Histopathologic Description: Cervical spinal cord: Microscopically, the lesions are characterized by a loss of myelin visible on HE-stained sections where the normally intense eosinophilia of the white matter is lost and the neuropil to has a fine fibrillar meshwork pattern dotted with numerous oligodendrocyte nuclei. With the Luxol fast blue stain, the deep blue color of the white matter is replaced by a light blue staining. A narrow rim of normal white matters is usually present between the edge of the lesion and the glial limitans, a characteristic sharp line of demarcation between the normal white matter and the lesion. The demyelination is associated with edema, swelling and splitting of myelin sheaths with gitter cells and a marked reactive astrocytosis. Only mild axonal changes (Wallerian degeneration) are seen, attesting axonal preservation. The vessels permeating the lesion are prominent and cuffed by mononuclear phagocytes.

Contributor's Morphologic Diagnosis: Cervical spinal cord: bilateral and often symmetrical demyelination in the dorsolateral funiculus, astrocytic hypertrophy and proliferation (astrocytosis, astrogliosis).

Disease name: Leukoencephalomyelopathy of the Rottweiler dog.

Contributor's Comment: Leukoencephalomyelopathy is a rare condition of the Rottweiler clinically beginning between 1.5 and 3.5-years-of-age, and characterized by a slow progressive ataxia, hypermetria and paresis of all four limbs, often beginning in the forelimbs, and late severe proprioceptive loss.[2,7] Generally no signs other than locomotor disturbances are observed.[7]

The main site of the lesions is the cervical spinal cord, which, on gross inspection, has dull white, opaque discoloration of the lateral (especially dorsal parts) and dorsal funiculi.[1,2] Lesions are bilateral with a characteristic more or less symmetric distribution. Histologic examination reveals lesions to be present also in the deep cerebellar white matter, brain stem, optic tracts and in other regions of the spinal cord.[7]
Microscopically, the lesions are characterized by a loss of myelin visible on HE-stained sections where the normally intense eosinophilia of the white matter is lost and the neuropil has a fine, fibrillar meshwork pattern dotted with

numerous oligodendrocyte nuclei. With the Luxol fast blue stain, the deep blue color of the white matter is replaced by a light blue staining. A narrow rim of normal white matter is usually present between the edge of the lesion and the glial limitans; a characteristic sharp line of demarcation between the normal white matter and the lesion. The demyelination is associated with edema, swelling and splitting of myelin sheaths with gitter cells and a marked reactive astrocytosis. Only mild axonal changes (Wallerian degeneration) are seen, attesting to axonal preservation. The vessels permeating the lesion are prominent and cuffed by mononuclear phagocytes.[1] In chronic lesions, many axons are invested by very thin sheaths which can be interpreted as indication of myelin regeneration.[6]

Transmission electron microscopic examination reveals irregular myelin splitting, thinning of myelin sheaths and naked axons, paucity of axonal organelles, absence of axonal swelling and neurofilament aggregates.[4]

The clinical differential diagnosis includes:

1. Neuroaxonal dystrophy: Progressive sensory ataxia in adult dogs characterized by head bobbing and positional nystagmus, with lesions of axonal spheroids, axonal degeneration and loss.
2. Canine distemper myelitis, characterized by high protein content and pleocytosis at CSF analysis.
3. Cervical spinal cord compression (wobbler syndrome): Myelography is required to exclude this possibility.

AFIP Diagnosis: Spinal cord, dorsal lateral funiculus: Demyelination, bilaterally symmetrical, diffuse, marked with gliosis (leukomyelopathy).

Conference Comment: The moderator offered guidelines for histologic differentiation of oligodendroglial cells, astrocytes and microglial cells. Oligodendroglial cells typically have a small, dense nucleus; astrocytes have a large nucleus with a nucleolus; and microglial cells have an elongate nucleus that often appears twisted.

Demyelination can be primary or secondary in nature. Primary demyelination results from direct damage to the myelin sheath with sparing of the axon. Secondary demyelination, the more common of the two types, occurs following axonal injury and loss.[8] Primary demyelinating diseases are rare animals; examples include canine distemper virus infection, caprine arthritis-encephalitis virus infection, hepatic encephalopathy and globoid cell leukodystrophy.[5] The process of demyelination begins with direct damage to oligodendroglia and/or the myelin sheath followed by release of lipids and myelin components into the extracellular space, activation of microglia and macrophage accumulation.[8]

Secondary demyelination frequently results from Wallerian degeneration. After damage to the nerve, degeneration and fragmentation of the axon and myelin occur at 24 and 48 hours, respectively. The proximal segment degenerates back to the first viable node of Ranvier while the distal segment dies. The cellular and myelin debris are phagocytosed by Schwann cells and macrophages. If the axon endoneurium has not been disrupted, regeneration ensues with the sprouting nerves entering the neural tube followed by remyelination by Schwann cells. Growth occurs at a rate of 1-4 mm per day.[8]

Unlike the peripheral nervous system, there is little regenerative potential within the central nervous system (CNS) due to a combination of the complex oligodendrocyte/axon relationship, the poor regenerative capacity of oligodendroglia, the absence of a basal lamina scaffold, and the inhibitory effect of myelin and lipid on axonal sprouting. Thus, demyelination in the CNS often results in the formation of an astroglial scar.[3]

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References:

1. Gamble DA, Chrisman CL: A leukoencephalomyelopathy of rottweiler dogs. *Vet Pathol*. 1984;21(3):274-80.
2. Jubb KVF, Huxtable CR. The nervous system. In: Jubb KVF, Kennedy PC, Palmer N, eds. *Pathology of Domestic Animals*. Vol. 1, 4th ed. San Diego, CA: Academic Press; 1993:373-374.
3. Maxie MG, Youssef S. Nervous system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:287-289.
4. Slocombe RF, Mitten R, Mason TA: Leucoencephalomyelopathy in Australian Rottweiler dogs. *Aust Vet J*. 1989;66(5):147-150.
5. Summers B, Cummings J, de Lahunta A. Principles of neuropathology. In: *Veterinary Neuropathology*. St. Louis, MO: Mosby; 1995:16-17.
6. Summers B, Cummings J, de Lahunta A. Degenerative diseases of the central nervous system. *Veterinary Neuropathology*. St. Louis, MO: Mosby; 1995:285-286.

7. Wouda W, van Nes JJ. Progressive ataxia due to central demyelination in Rottweiler dogs. *Vet Q*. 1986;8(2): 89-97.
8. Zachary JF: Nervous system. In: McGavin MD, Zachary JF, eds. *Pathologic Basis of Veterinary Disease*. 4th ed. St. Louis, MO: Elsevier; 2007:853-856,933.

CASE II: N2006-751 (AFIP 3073348).

Signalment: 9-year-old, female, white-fronted (parma) wallaby, marsupial (*Macropus parma*).

History: This wallaby had a several month history of progressive neurologic deficits, including ataxia and circling to the right, accompanied by weakness, muscle loss, and anorexia. She also had a history of lumbar vertebral spondylosis and dental abscess.

Laboratory Results: West Nile Virus, Wallaby retrovirus and *Toxoplasma* titers were negative. Radiographs, complete blood count and serum chemistries were non-diagnostic.

Gross Pathology: Near the right temporomandibular joint is an approximately 1.5 cm diameter abscess, which extends from the medial aspect of the mandibular ramus into the maxillary bone, through the calvarium and into the brain parenchyma. The abscess has a variably thick wall and the contents are pasty and grey-green with numerous small, firm, white-yellow flecks. Viewed from the ventral surface the brain is asymmetrical, with moderate expansion of the right caudal composite gyrus and pyriform lobe by an abscess that is contiguous with the abscess adjacent to the temporomandibular joint.

Histopathologic Description: Brain, cerebrum: Transverse section of the brain at the level of the interthalamic adhesion. Extending from the meningeal surface of the right ventrolateral cerebrum into the parenchyma is a large, 1.0 cm diameter, discrete focus of severe inflammation and necrosis creating a mass effect with thalamic midline shift to the left and herniation of the right cingulate gyrus under the falx cerebri (not visible in histologic sections; see submitted image). The mass is composed of dozens of irregularly shaped, large bacterial colonies surrounded by abundant degenerate neutrophils, fewer epithelioid and large foamy histiocytic cells, and peripherally by lymphocytes and plasma cells. The bacterial colonies are tangled mats of branched, filamentous to beaded bacteria surrounded by peripherally radiating homogeneous, acellular, brightly eosinophilic clubbed material (Splendore-Hoeppli reaction). The bacterial colonies are separated from each other by confluent areas of liquefactive necrosis. The adjacent brain parenchyma is rarefied, with numerous gitter cells. Blood vessels in the vicinity are variably surrounded by cuffs of lymphocytes and plasma cells 1-10 cells thick.

Special Stains:

- Gram stain (Brown and Brenn): Bacteria are gram positive
- Kinyoun Acid Fast: Bacteria are not acid fast

Note: While all slides clearly demonstrate the agent and inflammatory response described, the amount of brain parenchyma in the submitted slides is variable. Unfortunately, some slides contain processing artifacts as the tissue fragmented easily when cut.

Contributor's Morphologic Diagnosis: Brain: Pyogranulomatous meningoencephalitis, chronic, locally extensive, severe, with intralesional large filamentous, branching Gram positive and non-acid fast bacterial colonies surrounded by Splendore-Hoeppli reaction, consistent with *Actinomyces* spp.

Contributor's Comment: Lumpy jaw, or chronic alveolar osteomyelitis, is a common disease of marsupials belonging to the family Macropodidae (macropods), especially kangaroos and wallabies.[2,4,5,7] Unlike cattle, where the disease known as lumpy jaw is rather exclusively associated with *Actinomyces bovis*, in macropods the term is more inclusive and in the literature includes two general presentations,[2] one of which is associated with *Fusobacterium necrophorum* and the other with *Actinomyces* spp. Typically, lesions associated with *Fusobacterium necrophorum* (necrobacillosis) are necrotizing and/or purulent with acute inflammation of soft tissues, severe necrosis and lysis of the affected bone, fetid odor, and little periosteal new bone formation; this presentation is commonly reported in Australia.[2] By contrast, infection with *Actinomyces* spp. (actinomycosis) is a chronic infection characterized by excessive periosteal new bone formation, disfigurement of face, formation of draining tracts, and lacks the fetid odor and necrosis of *Fusobacterium* infections; this presentation is reported in zoos in the Northern

Hemisphere.[2] Both presentations can lead to significant mortality via starvation secondary to tooth loss, or septicemia/toxemia from bacterial infection. Lumpy jaw is more common in captive macropods than in free-ranging animals, but is not exclusively a disease of captivity.[5] In both captive and free living animals stress and crowding appear to be predisposing factors.[7] This discussion focuses mainly on actinomycosis.

Actinomyces spp. are commensal organisms of the mammalian oral cavity, found on mucus membranes and tooth surfaces.[1] Infection with this opportunistic pathogen begins with a traumatic break in the oral mucosa, potentially from tooth eruption, rough browse or other plant material. Infection becomes established in the alveolar or paralveolar tissues where bacterial colonies form and trigger a suppurative response in the immediate vicinity and mononuclear inflammation and fibrosis at the periphery. This process extends into the adjacent bone forming multiple small abscesses surrounded by granulation tissue and fibrosis, with lysis of bony trabeculae and excessive periosteal bone formation. This creates an expanded, yet porous bone that can best be seen on macerated specimens. Early lesions are very difficult to recognize without a thorough oral examination including dental radiographs. Histologic evaluation of early lesions demonstrates colonies of *Actinomyces*-like bacteria in the periodontal space, associated with alveolar bone resporption.[7]

The hallmark feature of *Actinomyces* infection is presence of "sulfur granules" scattered within the suppurative exudates.[1,8] Grossly, sulfur granules are yellow/white particles, varying in firmness, that are up to several millimeters in diameter. Histologically they are composed of characteristic 'club colonies' with brightly eosinophilic Splendore-Hoeppli reaction arranged as palisading clubs at the periphery of the bacterial colonies.[1,8] Splendore-Hoeppli material is proposed to be aggregates of antigen-antibody complexes, and although it is not exclusive to a particular agent (it can be seen in some bacterial, fungal and parasitic infections as well as occasionally with foreign bodies) its presence is diagnostically helpful. Bacterial pathogens that commonly elicit this tissue response are few, and in animals these include *Actinobacillus lignieresii* (wooden tongue), *Staphylococcus aureus* (botryomycosis), and *Nocardia* spp. Bacterial morphology and special stains are then useful in distinguishing between these agents. Of these bacteria, only two are branching filamentous bacteria (as seen in this case): *Actinomyces* and *Nocardia*. Both *Actinomyces* and *Nocardia* are Gram positive, but only *Nocardia* is weakly acid fast.[1] In this case, *Actinomyces* was not cultured from the jaw abscess; however, the characteristic histomorphology (mats of branching filamentous bacteria) and staining patterns of the bacterial colonies (Gram positive and non-acid fast) was highly suggestive of *Actinomyces* spp. Most often, the lesions of "lumpy jaw" contain mixed bacterial populations due to overgrowth or invasion of other commensal oral flora. The best chance of isolating *Actinomyces* is with submission of sulfur granules for bacterial culture.[4] *Actinomyces bovis* and *A. viscosus* have been isolated from macropods with lumpy jaw.[7]

Alveolar actinomycosis is a chronic, disfiguring disease that is difficult, if not impossible, to cure. The causative agent, a Gram-positive bacterium, is susceptible to penicillin antibiotics; however, tissue penetration is problematic given the degree of fibrosis and potential persistence of bacteria within dentin tubules of affected teeth[3]. Other treatments reported include draining and flushing the lesion with sodium iodide,[2] hydrogen peroxide or sodium hypochlorite,[4] and removal of the apex of the tooth root with endodontic filling.[4]

The peculiar susceptibility of macropods to chronic alveolar osteomyelitis may be related to a process known as molar progression, and the propensity for accumulation of calcified deposits on the molar and premolar teeth.[7] Molar progression is a feature of many, but not all, macropods and is thought to optimize the processing of plant material in the dental mill. It is the mesial (forward and medial) movement of molariform teeth along the jaw with age. In tammar and parma wallabies molar progression is primarily due to the growth and resultant forward movement of the bones bearing the teeth ("mesial shift") rather than the forward movement of the teeth relative to the supportive bone ("mesial drift").[6] The result is the formation of 'post functional' molariform teeth that no longer contribute to mastication of food and are subsequently shed. Before being shed, these teeth often manifest alveolar bone loss and food impaction. Macropods are also prone to development of abundant dental calculus on their teeth. This is likely due to the high phosphate content of their saliva, pH of 6-8, and large numbers of *Bacterionema matruchottii*,[7] which promote plaque formation and bone resorption. Both of these processes can create defects in the oral mucous barrier integrity and an environment favorable to colonization by the causative bacteria of both presentations of lumpy jaw in macropods - *Actinomyces* and *Fusobacterium necrophorum*. In macropods the mandible and maxilla appear equally affected by alveolar osteomyelitis, whereas the lesion in cattle is predominantly mandibular with the maxilla rarely involved.[2,8]

Secondary lesions of chronic alveolar osteomyelitis in macropods include tooth loss, deformation of the affected bone, and local extension into the palatine bones and nasal cavities,[2,7] but the local extension through the calvarium

and into the brain, as seen in this case, is a rare occurrence. The involvement of the right rostral thalamus in the resultant brain lesion correlates well with the clinical signs of propulsive circling to the right ("adversive syndrome").[3] Other routes of infection were considered in this case; however, there was no evidence of external skull or facial trauma or puncture wounds to suggest traumatic inoculation of bacteria, and no evidence of otitis to suggest local extension from the ear. Histologic examination of the right maxilla revealed multiple foci of chronic alveolar osteomyelitis with *Actinomyces*-like bacteria (identical to the colonies seen in the brain lesion) in the area of the periodontal ligament near the apex of the tooth root and within the maxillary bone, supporting the proposed origin of the brain abscess as local extension of maxillary alveolar osteomyelitis.

AFIP Diagnosis: Brain: Meningoencephalitis, pyogranulomatous, focally extensive, severe with mild multifocal perivascular meningitis, large colonies of filamentous bacilli, and Splendore-Heoppli material (sulfur granules).

Conference Comment: As noted by the contributor, there is slide variation in the amount of tissue present for evaluation and frequent tissue artifact. The contributor provides an excellent review of actinomycosis in macropods, with particular emphasis on the clinical signs, disease course and pathogenesis.

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References:

1. Bilberstein EL, Hirsh DC. Filamentous bacteria: actinomyces, nocardia, dermatophilus, and streptobacillus. In: Hirsh DC, MacLachlan NJ, Walker RL, eds. *Veterinary Microbiology*. 2nd ed. Ames, IA: Blackwell Publishing; 2004:215-222.
2. Butler R. Montremes and Marsupials (Monotremata and Marsupialia), bacterial diseases. In: Fowler ME, ed. *Zoo and Wild Animal Medicine*. 2nd ed. Philadelphia, PA: WB Saunders Company; 1986:572-576.
3. De Lahunta A. Diencephalon. In: De Lahunta A, ed. *Veterinary Neuroanatomy and Clinical Neurology*. 2nd ed. Philadelphia, PA: WB Saunders Company; 1983:344-355.
4. Fagan DA, Oosterhuis JE, Benirschke K. "Lumpy jaw" in exotic hoofstock: A histopathologic interpretation with treatment proposal. *J Zoo Wildl Med*. 2005;36(1):36-43.
5. Griner, LA. Marsupialia. In: Griner LA, ed. *Pathology of Zoo Animals*. San Diego, CA: Zoological Society of San Diego; 1983:301-309.
6. Lentle RG, Hume ID, Stafford KJ, Kennedy M, Haslett S, Springett BP. Molar progression and tooth wear in tammar (*Macropus eugenii*) and parma (*Macropus parma*) wallabies. *Australian Journal of Zoology*. 2003;51:137-151.
7. Miller WA, Beighton D, Butler R. Histological and osteological observations on the early stages of lumpy jaw. In: Montali RJ, Migaki, G, eds. *The Comparative Pathology of Zoo Animals, Proceedings from the Symposia at the National Zoological Park, 1978*. Washington, DC: Smithsonian Institution Press; 1980:231-239.
8. Palmer N. Bones and joints. In: Jubb KVF, Kennedy PC, Palmer N, eds. *Pathology of Domestic Animals*. 4th ed. Vol 1. San Diego, CA: Academic Press; 1993:106-108.

CASE III: 09-7191 (AFIP 3164121

Signalment: Eleven year-old, castrated male, Scottish terrier, canine (*Canis familiaris*).

History: The dog had bouts of vomiting with elevated liver enzymes and atypical Cushing's disease of 3 weeks duration. There was a 3-day history of vestibular/cerebellar disease and fever. A cerebrospinal fluid analysis had 20 cells (mostly eosinophils). The MRI was normal. The disease progressed to the point of the patient becoming non-ambulatory. The dog did not improve with corticosteroid and cyclosporine treatment and was euthanized.

Gross Pathology: There were no gross lesions reported by the submitting veterinarian.

Histopathologic Description: Brain: In sections of cerebral cortex, basal ganglia, midbrain, cerebellum and medulla there are multifocal areas of malacia containing aggregates of foamy macrophages in areas of disrupted neuropil. Blood vessels are cuffed by inflammatory cells including many eosinophils mixed with lymphocytes, plasma cells and macrophages. Perivascular cuffs of similar composition are present in the overlying meninges.

Cross sections of nematode parasites with a cuticle, prominent lateral alae, paired triangular-shaped excretory columns and a digestive tract occur in areas with inflammation and without.

Contributor's Morphologic Diagnosis: Encephalitis, granulomatous and eosinophilic, subacute, multifocal, severe with intralesional nematodes. (Etiology: *Baylisascaris* spp.)

Contributor's Comment: *Baylisascaris procyonis,* the raccoon ascarid roundworm, causes central nervous system (CNS) disease in over 45 species of animals including dogs and humans.[4] Reported cases in dogs have all been puppies exposed to fecal material of raccoons that were housed in close proximity.[4,5]

The raccoon sheds eggs of the parasite in the feces. The eggs are resistant and can survive for years in the environment. They require two to four weeks to mature to the infective stage. Dogs, a susceptible aberrant host, are infected by consuming eggs from a contaminated environment followed by visceral migration of the larvae, some of which enter the brain and cause damage and clinical disease.[4]

The parasite causes a severe inflammatory reaction and physical damage because of its large size and aggressive migration.[1] A rapid clinical course, peripheral eosinophilia, and eosinophlic pleocytosis of the cerebrospinal fluid are highly suggestive of *Baylisascaris* larval migration in the central nervous system (CNS).[4] Treatment with anthelmenthics is not usually effective and the prognosis is guarded in all cases. Corticosteroids are administered in an attempt to decrease the inflammatory process associated with parasite migration and may result in some clinical improvement.

AFIP Diagnosis: Brain, cerebrum: Meningoencephalitis, eosinophilic and lymphohistiocytic, multifocal, mild to moderate with necrosis, gliosis, gitter cells, and rare larval nematodes.

Conference Comment: Participants commented on the slide variation, with some sections having prominent nematode larvae and others almost devoid of parasites. The moderator pointed out that eosinophilic and lymphohistiocytic inflammation, gitter cells, and random, "punched-out" holes of necrosis strongly suggest aberrant parasitic migration, regardless of the lack of parasites in tissue sections. Most participants favored *Baylisascaris procyonis* as the etiologic agent; the moderator likewise favored *B. procyonis* based on the size of the nematode and the frequency of occurrence in the CNS of the dog. This generated discussion of other parasites which undergo aberrant migration through the CNS of animals. The following chart summarizes the entities discussed:[2,3]

Parasite	**Natural Host**	**Aberrant Host**
Coenurus cerebralis (larval stage of *Taenia multiceps*)	Dog, wild carnivores	Sheep, horse, other herbivores, man
Cysticercus cellulosae (larval stage of *Taenia solium*)	Humans	Pig, dog
Parastrongylus (*Angiostrongylus*) *cantonensis*	Rat	Dog, man
Parelaphostrongylus tenuis	White-tailed deer	Sheep, red deer, elk, moose
Elaphora schneideri	Mule deer, black-tailed deer	Sheep, goat, elk, moose, sika deer, white-tailed deer JKP, vol 3, pg 92
Setaria digitata	Cow, buffalo	Horse, camel, sheep, goat
Halicephalobus gingivalis	Free-living	Horse
Angiostrongylus vasorum	Dog	Dog
Stephanurus dentatus	Pig	Pig
Strongylus spp.	Horse	Horse
Dirofilaria immitis	Dog	Dog, cat
Cuterebra cerebralis	Rodent, rabbit	Cat, dog

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References:

1. Kazacos KR, Boyce WM. *Baylisascaris* larva migrans. *J Am Vet Med Assoc*. 1989;195:894-903.
2. Maxie MG, Robinson WF. Cardiovascular system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:92.
3. Maxie MG, Youssef S. Nervous system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:438-439.
4. Rudman DG, Kazacos KR, Storandt ST, Harris DL, Janovitz EB. *Baylisascaris procyonis* larva migrans in a puppy: A case report and update for the veterinarian. *J Am Anim Hosp Assoc*. 1996;32:73-76.
5. Thomas JS. Encephalomyelitis in a dog caused by *Baylisascaris* infection. *Vet Pathol*. 1988;25:94-95.

CASE IV: 10-8794103 (AFIP 3176070).

Signalment: 12-week-old, intact male, Kelpie puppy, canine (*Canis familiaris*).

History: The puppy presented with acute onset of ataxia and tremors; signs only became apparent in the past few days. The owner has 5 of the 10 puppies of this litter: 2 males and 3 females. All 3 females and this male were showing clinical signs; the male was the worst affected. The other 5 pups owned by someone else were apparently all fine.

Gross Pathology: No gross abnormalities were seen in the brain of this puppy.

Laboratory Results: Cerebrospinal fluid analysis:

Appearance	Colorless and clear
Microscopy	
Erythrocytes	1500 x 10^6/L
Leucocytes	7 x 10^6/L
Gram stain	No bacteria or protozoal organisms seen
Chemistry	
Protein	0.30 g/L (0.10-0.33)
Cytology	Cytospin: few mononuclear cells & rare neutrophils Insufficient cells for differential count. Minimal hemorrhage
Interpretation:	No significant abnormalities

Histopathologic Description: Brain, cerebellum: Multifocally and segmentally, there is degeneration and loss of Purkinje cells, with rare discrete clear spaces in the Purkinje cell layer (empty baskets). In some of the folia, there is almost complete absence of the Purkinje cell layer. Multifocally, remaining Purkinje cells are shrunken, angular and hypereosinophilic with karyolysis or pyknosis (necrosis), or swollen and finely vacuolated with dispersal of Nissl substance (chromatolysis). More severely affected regions have mild spongiotic change affecting the inner aspect of molecular layer neuropil associated with proliferation of Bergmann's astrocytes (gliosis). Multifocally, there is thinning of the inner granular cell layer, with patchy hypocellularity and scattered individual granular neurons with pyknotic nuclei. Rarely, swollen Purkinje cell dendrites extend into the molecular layer (torpedoes). Multifocally within the white matter of the cerebellar folia, there is mild Wallerian-type degeneration, with scattered discrete round clear vacuoles containing individual phagocytes (Gitter cells) and occasional slightly swollen, hypereosinophilic axons (spheroids).

Contributor's Morphologic Diagnosis: Brain, cerebellum: Purkinje cell degeneration, necrosis and loss, multifocal to segmental, moderate, with secondary granular cell loss and mild white matter Wallerian degeneration

Contributor's Comment: Abiotrophy refers to a premature or accelerated degeneration of formed elements; this differs from hypoplasia, in which an organ fails to form completely during development.[4,18] Once developing neurons are differentiated, they do not further divide, and having completed development, are expected to endure for the lifetime of an individual.[4] Premature neuronal degeneration reflects an intrinsic abnormality in cellular structure, with altered metabolic activity resulting in unexpected degeneration.[4,8] In some cases, neuronal abiotrophy is apparent as overt cell loss within localized or multiple brain compartments; other cases may have more subtle changes in neuronal cell body, processes, or myelin sheath, leading to neuronal circuit dysfunction.[8] The term

abiotrophy describes the pathological process of neuronal degeneration, but does not provide a clue to the underlying mechanism.[4,12,18] In most instances, the specific cellular defect is unknown; however, postulated theories include glutamate receptor excitotoxicity, channelopathies and autoantibody-mediated disorders.[1,4,6-8,11]

One of the most common of the domestic animal neuronal abiotrophies is that which affects the cerebellar cortex. Most of these are limited to the Purkinje neurons, which appear to be excessively susceptible to such intrinsic disturbances of their metabolic apparatus.[4,7] Where sufficient numbers of affected animals have been studied, autosomal recessive inheritance has been proven or implicated in most cases; however, X-linked cerebellar ataxia has been reported in the English pointer, and an unusual case of cerebellar Purkinje's cell degeneration associated with coat color dilution in Rhodesian ridgebacks was also reported.[3,4,8] Moreover, in a few cases of late (adult) onset cerebellar degeneration, extrinsic factors have also been considered as a possible underlying cause.[4,6,10] Indeed, some authors have made the distinction between cerebellar abiotrophy and cerebellar cortical degeneration (CCD) with abiotrophy defined as a proven inherited disease.[1,2,4,18]

Cerebellar abiotrophy has been reported in various domestic species including: dogs, cats, sheep, cattle, pigs, and horses.[4] The condition occurs in numerous dog breeds, including, but not limited to: Beagle, Samoyed, Old English Sheepdog, Gordon Setter, Border Collie, Rough-coated Collie, Finnish Terrier, Scottish Terrier, Brittany Spaniel, Labrador Retriever, Airedale, Lagotto Romagnolo, Rhodesian ridgeback, American Staffordshire Terrier, and Miniature Schnauzer.[1-4,6,7,10,11,14-17,19] Each breed appears to possess a different phenotype with respect to the range of signs shown, age of onset, and rate of progression, suggesting differing genetic etiologies in different breeds.[17]

Animals with cerebellar abiotrophy may show signs of dysfunction at birth or during early ambulation (neonatal abiotrophy), but it is more usual to be born with normal neurologic function followed by delayed onset of clinical signs ranging from a few weeks to several years of age, corresponding to the onset of neuronal degeneration (postnatal abiotrophy).[8] At one end of the scale, such as in Labrador Retrievers and Border Collies, signs are seen at an early age (6 to 12 weeks), with rapid progression (few weeks). In contrast, Gordon Setters do not usually present with signs until 6 months to 2 years of age, and progression is slow (months to years); and most affected American Staffordshire Terriers are recognized between 4 to 6 years of age.[8] Brittany Spaniels have the latest onset of cerebellar signs (average age of 10 years) with similar slow progression.[1,8]

Clinical signs (ataxia, intention tremor, hypermetria/spasticity, proprioceptive deficits, wide-based stance, stumbling/falling) reflect the loss of function of inhibitory cerebellar cortical neurons, resulting in abnormal range, rate and force of voluntary movements.[7] Other clinical findings may include loss of menace reflex and nystagmus.[1-3,7,10] The disease and clinical signs are usually progressive, although in some cases affected animals reach a stage at which clinical signs will plateau. Moreover, there is suggestion that affected animals may learn over time to partially compensate for their deficit. In some breeds, e.g. Brittany Spaniel, severity of cerebellar signs does not seem to correlate with the often minimal degree of histopathologic abnormality.[8]

In most cases, definitive diagnosis can only be made at necropsy by histopathological examination, although MRI has been used a diagnostic tool to demonstrate cerebellar atrophy.[5,6,10,17,18] Grossly, the cerebellum of affected animals may exhibit no overt abnormality, or may be smaller than normal, sometimes with slight flattening or narrowing of the folia.[2,19] For example, a normal dog's cerebellum accounts for approximately 10 to 12 per cent of the brain's mass, versus 5 to 7% in some studies.[6,7,10]

The most significant histopathological finding in cerebellar cortical abiotrophy usually is depletion of Purkinje cells.[6,10,18] These neurons complete their migration and differentiation during gestation, whereas granule cell development is not complete until approximately 10 weeks postnatally in the dog and cat.[8,19] Because the integrity of the granule cell neuron is dependent on its synaptic relationship with the dendritic zone of the Purkinje cell, loss of the latter neuron usually results in a secondary depletion of granule cell neurons.[4,7,11,19] There may also be atrophy of the molecular layer. The histological picture has been similar for dogs of the same breed, often with specific regional distribution and severity.[2,6,19] For example, in the Scottish Terrier changes are most pronounced within the dorsal cerebellum and less severe ventrally, with relative sparing of the nodulus and uvula.[17]

Other regions of the brain are often normal; however, multisystem neuronal abiotrophies involving degeneration of extrapyramidal nuclei and other motor systems have been reported.[8] In Kerry Blue Terriers, Purkinje and granule cell degeneration is followed by degeneration of olivary nuclei, then the caudate nucleus and substantia nigra, possibly reflecting a form of transsynaptic degeneration.[4,8] In some cases, granule cell degeneration appears to occur first, followed by Purkinje cell loss, e.g. Rough-coated Collie, or with sparing of the Purkinje cells, e.g. Lagotto Romagnolo, Brittany Spaniel and Border Collie.[6,15]

Cerebellar abiotrophy was first reported in the Australian Kelpie in 1989 by Thomas & Robertson.[16] A prospective breeding trial was conducted after a dog breeder reported several pups with signs of cerebellar disease. Affected pups have normal mental alertness and exhibit clinical symptoms from 5-6 weeks of age, including: mild, non-progressive to severe ataxia, hypermetria, proprioceptive deficits and head tremor, without accompanying weakness.[16] Fitting has been observed in some dogs.[13] Although the onset of degeneration appears to be prior to 6 weeks of age, there is variation in clinical signs and mildly affected dogs may not be identified until several months of age.[16] Histological lesions are confined to the cerebellum, most commonly and severely within the anterior lobules of the vermis and characterized by regional loss of Purkinje cells, marked reduction in granular cell density, and mild spongiosis and Wallerian degeneration in the white matter tracts of affected folia.[16]

All affected animals can be traced back to a small number of related common ancestors within eight generations. These dogs featured prominently in sheep dog trials and thus had been widely used for breeding, increasing the likelihood of increased disease incidence.[16] The disease is thought to be due to a single mutation amplified by using a popular sire in a small gene pool and inbreeding. Affected dogs should be homozygous, identical-by-descent, and close to the mutation.[13] Three candidate genes (SETX2, ATCAY3 and SYNE14) that are known to cause cerebellar abiotrophy in humans were tested and subsequently excluded as the candidate gene in Kelpies by homozygosity analysis.[13]

Dr Allan Wilton of the University of NSW, in collaboration with the Working Kelpie Council of Australia, is working toward developing a genetic test for the cerebellar abiotrophy mutation in Kelpies (also referred to as 'ataxia'). Blood spot collection kits (sampling from dogs' ears) have been developed and distributed to dog breeders for subsequent DNA analysis utilizing microarray technology.

AFIP Diagnosis: Brain, cerebellum: Purkinje cell degeneration, necrosis and loss, multifocal and segmental, moderate, with granular cell loss and Purkinje and granular layer gliosis.

Conference Comment: The contributor provides a detailed review of cerebellar abiotrophy in the dog, with particular attention paid to the Australian Kelpie. Conference participants also commented on the presence of an external granular cell layer in the cerebellum of this case; most were of the opinion that this is not a typical histologic finding for a normal 12-week-old-dog. The external granular cell layer arises from germinal cells which migrate to the surface of the cerebellar folia. Here, the cells proliferate, differentiate into various microneurons e.g. basket cells, stellate cells, and granule cells, and migrate to their final location. This process begins in late gestation and continues for a couple of weeks after birth.[9] Failure of the microneurons to establish orderly synaptic connections results in cellular disorganization of the cerebellum.[9] Whether the presence of an external granular cell layer is associated with the disease process in the case of this Kelpie puppy is unknown; the feature is not described in the literature. Retention of the external granular granule cell layer in this puppy may reflect the disease variability inherent in cases of cerebellar abiotrophy.

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References:

1. Berry ML, Blas-Machado U. Cerebellar abiotrophy in a miniature schnauzer. *Can Vet J*. 2003;44(8):657–659.
2. Bildfell RJ, Mitchell SK, de Lahunta A. Cerebellar cortical degeneration in a Labrador retriever. *Can Vet J*. 1995;36(9):570-572.
3. Chieffo C, Stalis IH, Winkle TJ, Haskins ME, Patterson DF. Cerebellar Purkinje cell degeneration and coat color dilution in a family of Rhodesian Ridgeback dogs. *J Vet Intern Med*. 1994;8(2):112-116.
4. de Lahunta A. Abiotrophy in domestic animals: A review. *Can J Vet Res*. 1990;54(1):65-76.
5. Henke D, Böttcher P, Doherr MG, Oechtering G, Flegel T. Computer-assisted magnetic resonance imaging brain morphometry in American Staffordshire terriers with cerebellar cortical degeneration. *J Vet Intern Med*. 2008;22 (4):969-975.
6. Jokinen TS, Rusbridge C, Steffen F, et al. Cerebellar cortical abiotrophy in Lagotto Romagnolo dogs. *J Small Anim Prac*. 2007;48(8):470-473.
7. Kent M, Glass E, deLahunta A. Cerebellar cortical abiotrophy in a beagle. *J Small Anim Prac*. 2000;41(7): 321-323.
8. March PA. Degenerative brain disease. *Vet Clin North Am Small Anim Pract*. 1996;26(4):945-971.
9. Maxie MG, Youssef S. Nervous system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:310-312.

10.Olby N, Blot S, Thibaud JL, et al. Cerebellar cortical degeneration in adult American Staffordshire terriers. *J Vet Intern Med*. 2004;18(2):201-208.
11.Sandy JR, Slocombe RF, Mitten RW, Jedwab D. Cerebellar abiotrophy in a family of border collie dogs. *Vet Pathol*. 2002;39(6):736-738.
12.Shamir M, Perl S, Sharon L. Late onset of cerebellar abiotrophy in a Siamese cat. *J Small Anim Prac.* 1999;40 (7):343-345.
13.Shearman JR, Lau VM, Wilton AN. Elimination of SETX, SYNE1 and ATCAY as the cause of cerebellar abiotrophy in Australian Kelpies. *Anim Genet*. 2008;39(5):573.
14.Steinberg S, Van Winkle T, Bell JS, de Lahunta A. Cerebellar degeneration in Old English Sheepdogs. *J Am Vet Med Assoc*. 2000;217(8):1162-1165.
15.Tatalick LM, Marks SL, Baszler TV. Cerebellar abiotrophy characterized by granular cell loss in a Brittany. *Vet Pathol*. 1993;30(4):385-388.
16.Thomas JB, Robertson D. Hereditary cerebellar abiotrophy in Australian Kelpie dogs. *Aust Vet J.* 1989;66(9): 301-302.
17.Urkasemsin G, Linder KE, Bell JS, de Lahunta A, Olby NJ. Hereditary cerebellar degeneration in Scottish terriers. *J Vet Intern Med*. 2010;24(3):565-570.
18.Van der Merwe LL, Lane E. Diagnosis of cerebellar cortical degeneration in a Scottish terrier using magnetic resonance imaging. *J Small Anim Prac*. 2001;42(8):409-412.
19.Yasuba M, Okimoto K, Iida M, Itakura C. Cerebellar cortical degeneration in beagle dogs. *Vet Pathol*. 1988;25 (4):315-317.