**The Armed Forces Institute of Pathology**
**Department of Veterinary Pathology**

**WEDNESDAY SLIDE CONFERENCE 2007-2008**

# Conference 21

**2 April 2008**

*Moderator*:

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**CASE I – 05-317 (AFIP 3026796).**

**Signalment:** Five-month-old, female, Yorkshire terrier, canine

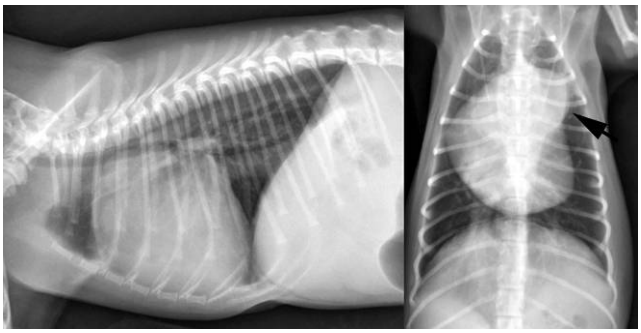
**History:** Presented to referring veterinarian at 3 months of age with V/VI continuous murmur.
Referred to University of Tennessee Veterinary Teaching Hospital 2 months later:

- Dyspnea - RR 40 bpm - Increased bronchovesicular sounds
- HR 132 bpm, no murmur at this time
- Vulvar mucosa gray-pink
- Lethargy, Weakness, Anorexia

Radiographs: Right-sided cardiomegaly with enlarged right pulmonary artery segment **(Fig. 1-1)**
Echocardiogram and Doppler measurements used to estimate pulmonary artery pressures:

- Patient = 74 mmHg Systolic, 42 mmHg Diastolic (Pulmonary hypertension)
- Normal = 20 to 25 mmHg, 8 to 10 mmHg
- Severely dilated RA and RV
- Severely dilated proximal pulmonary artery
- Decreased LV and LA filling

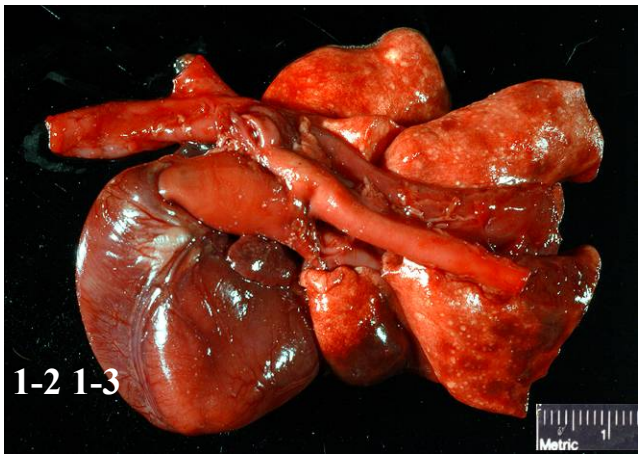
First Pass Cardiac Nuclear Scintigraphy: Cephalic vein bolus injection traced first to right atrium and then to liver and other abdominal organs - very little went to the lungs - interpreted to reflect high magnitude right to left shunt.

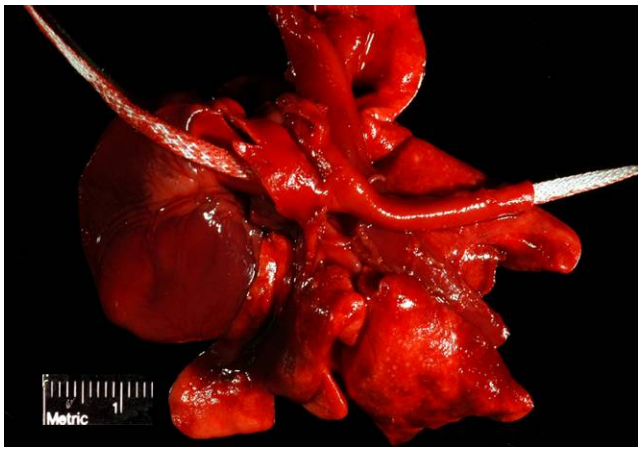


*1-1 Thoracic radiograph, Yorkshire terrier. Right-sided cardiomegaly with enlarged right pulmonary artery segment.*

*Radiograph courtesy of University of Tennessee College of Veterinary Medicine, Department of Pathobiology, Knoxville, TN 37996-4542, http://www.vet.utk.edu/departments/path/*

Patient was euthanized after developing apnea and bradycardia. Necropsy was delayed due to scintigraphy study, resulting in some autolysis. Owners requested cosmetic exam restricted to thorax.




*1-2 Heart, great vessels and lungs, Yorkshire terrier. The right atrium and ventricle and main pulmonary artery segment are markedly dilated. Patent ductus arteriosus (PDA) is present approximately 2 cm from the heart base.*
*1-3 Heart, great vessels and lungs, Yorkshire terrier. Patent ductus arteriosus.*

*Gross photographs courtesy of University of Tennessee College of Veterinary Medicine, Department of Pathobiology, Knoxville, TN 37996-4542, http://www.vet.utk.edu/departments/path/*

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**Gross Pathology:** Two ml of a clear red-tinged fluid was present in the pericardial sac. The right atrium and ventricle were markedly dilated, the right auricle approximately 2-3 times the size of the left. The main pulmonary arterial segment (PAS) was greatly dilated with a diameter of approximately 1 cm extending 2 cm from the heart base to the area of the patent ductus arteriosus (PDA) where the PAS and proximal descending aorta appeared to be fused from the exterior aspect **(Fig. 1-2).** The connection between the two vessels was 0.33 cm externally and the internal diameter was approximately 3 mm **(Fig. 1-3)**. Distal to the PDA the pulmonary artery narrowed abruptly entering the lung.

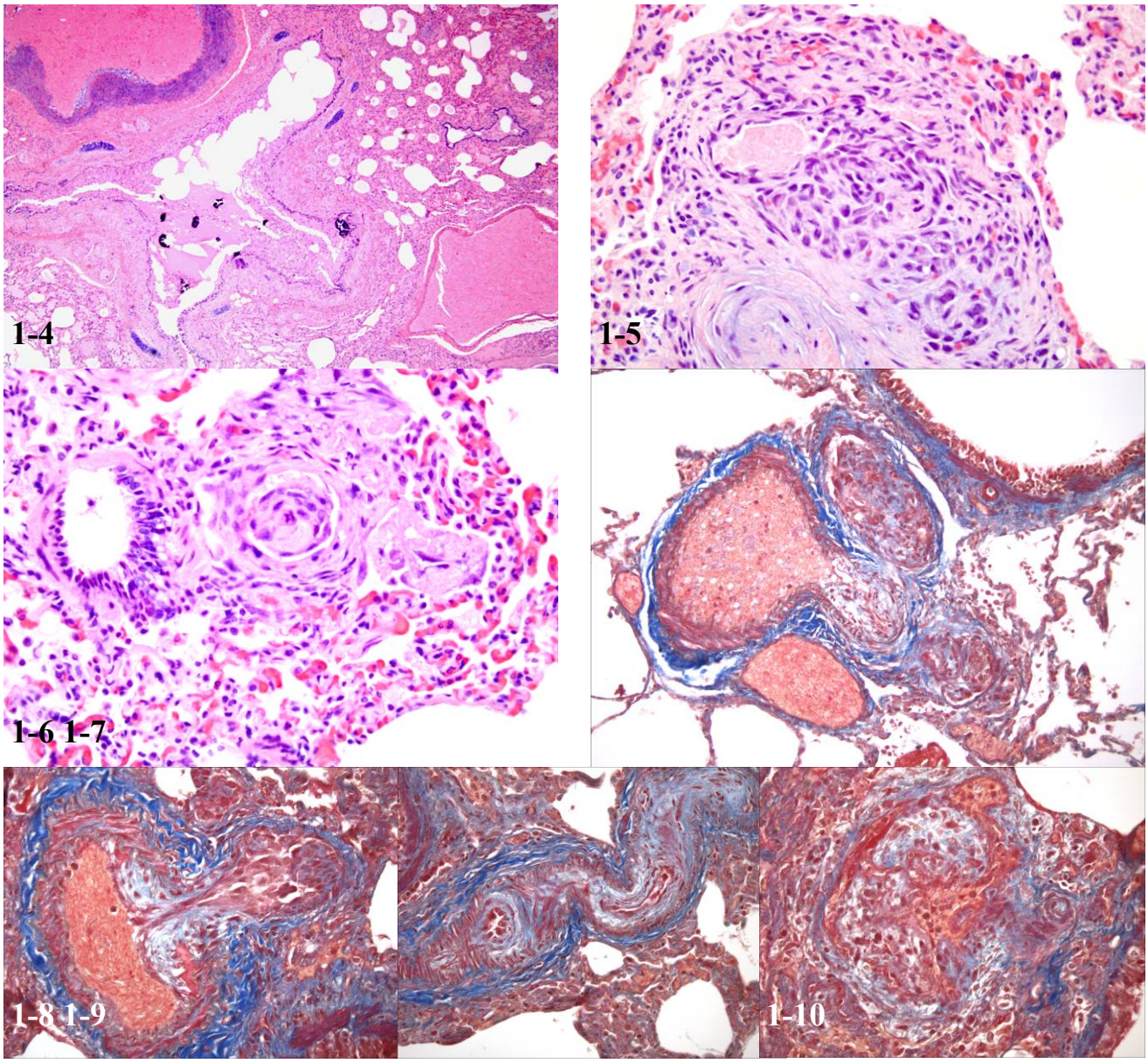
**Laboratory Results:**
CBC, blood glucose, electrolytes and coagulation panel unremarkable except for low platelet count
Urinalysis: SG 1.019, pH 5.5, 2+ proteinuria, 0-1 WBC/hpf, 1-3 RBC/hpf, many granular casts, trace bacteria

**Histopathologic Description:**
Lung: There are scattered areas of soft tissue mineralization (alveolar walls, bronchial basement membranes) with some emphysema, edema, proliferation of type II pneumocytes and accumulation of alveolar macrophages **(Fig. 1-4)**. Some large to medium sized pulmonary arteries contain asymmetric areas of intimal thickening and basophilia (reactive myxomatous matrix) or dense proteinic eosinophilia **(Fig. 1-5, 1-6)**. Scattered smaller arteries have segmental areas of intimal to medial basophilia or marked smooth muscle thickening of the wall - in some cases vessels are largely obscured by knots of proliferating plump spindle cells, sometimes forming capillaries (fibroblasts and/or endothelium) and sometimes forming bulging "masses" apparently at branch points. Trichrome stains reveal alveolar wall collagen deposition in scattered areas, sometimes associated with emphysema, increased collagen around some affected small arteries and the fibrotic nature of intimal proliferative lesions **(Fig. 1-7, 1-8, 1-9, 1-10)**.

**Contributor's Morphologic Diagnosis:**
1. Marked multifocal pulmonary arterial intimal sclerosis and medial hypertrophy with fibro-endothelial proliferation
2. Mild multifocal alveolar fibrosis and emphysema
3. Moderate multifocal bronchial and alveolar mineralization

**Contributor's Comment:** The clinical and necropsy findings, including pulmonary arterial lesions, are essentially identical to those described by J.W. Buchanan in dogs with hereditary PDA and a right to left pressure gradient.[2] The clinical work up clearly indicated a right to left shunting of blood flow in this case. There are two possible explanations for this right to left pressure gradient in the context of a PDA:

1. The pulmonary vasculature does not respond (dilate) as it should at birth, with inflation of the lung, and the prenatal pressure gradient from right heart to left is maintained after birth.




*1-4. Lung, vessel, Yorkshire terrier. There is multifocal mineralization within the large caliber vessel walls and within bronchial subepithelial connective tissue. Occasional mineralized concretions are within the bronchial lumen. (HE 40 X).*
*1-5. Lung, vessel, Yorkshire terrier. Focally mature plexiform lesions characterized by endothelial proliferation admixed with tightly packed vasoformative cell proliferation and extracellular matrix proliferation and occludes the lumen. (HE 400X)*
*1-6. Lung, vessel, Yorkshire terrier. Multifocally within intra-acinar arterioles there is concentric nonlaminar medial hypertrophy and intimal thickening which occludes the lumen. (HE 400X).*
*1-7, 1-8, 1-9, 1-10. Lung, Yorkshire terrier. Increased collagen around some affected small arteries and the fibrotic nature of intimal proliferative lesions is demonstrated using trichrome stain. (Trichrome stain).*

*Fig. 1-7 to 1-10 courtesy of University of Tennessee College of Veterinary Medicine, Department of Pathobiology, Knoxville, TN 37996-4542, http://www.vet.utk.edu/departments/path/*

2. After birth the normal shift in pressure gradient occurs across the ductus and shunting of blood across the PDA from the left to right outflow tracts results in increased circulation through the pulmonary vasculature. Eventually this over-circulation induces arterial sclerosis, hypertension and reversal of the gradient across the ductus from right to left.

While either scenario is possible with this clinical presentation, the histologic arterial changes and pulmonary arterial pressures, as per analysis of echocardiograms, are more consistent with the latter. The vascular lesions in the lung are most consistent with a reactive change and would also exacerbate the progression of hypertension over time. The distinct murmur detected at 3 months of age and absent 2 months later, just before euthanasia, likely reflects this dynamic process as hypertension developed and resulted in changes in blood flow through the ductus.

The etiology of pulmonary mineralization is most likely related to azotemia. Urinalysis suggested significant tubular damage but BUN and creatinine values were not available and kidneys were not examined because necropsy was restricted to the thorax.

**AFIP Diagnosis:** 1. Lung, artery: Pulmonary arteriopathy characterized by subintimal and medial hypertrophy, intimal fibrosis and cellular thickening, plexiform lesions, and arteritis, Yorkshire terrier (*Canis familiaris*), canine.
2. Lung: Mineralization, interstitial, vascular, multifocal.
3. Lung: Edema, multifocal, moderate.

**Conference Comment**: Pulmonary hypertension occurs when the mean pulmonary arterial pressure is greater than 25 mm Hg at rest or more than 30 mm Hg during exercise.[9,13] Secondary pulmonary hypertension may occur following conditions that lead to increased left atrial pressure or increased pulmonary vascular resistance (heartworm disease, chronic respiratory disease, thromboembolism, and vascular remodeling).[5,6,8] Primary pulmonary hypertension on the other hand is defined as pulmonary hypertension of unknown cause.[3,6]

Pulmonary arteriopathy (plexogenic pulmonary arteriopathy) is a condition characterized by constrictive and complex, obstructive, and proliferative vascular lesions in the pre- and intra-acinar pulmonary arteries that results in pulmonary arterial hypertension and eventually right-sided heart failure.[20] Pulmonary arterial hypertension with pulmonary arteriopathy can be subdivided into idiopathic, familial and associated with risk factors or conditions. Most cases in dogs have been idiopathic or associated with congenital heart disease, particularly patent ductus arteriosus.[9,16] Histologic lesions include plexiform lesions of the small arterioles with concentric intimal cellular proliferation and fibrosis, non-specific medial hypertrophy, muscularization of arterioles, fibrinoid degeneration and arteritis.[1,2,7,9,15,16] The association between pulmonary hypertension and the development of pulmonary arteriopathy is not fully understood as each may contribute to the formation of the other.

The pathogenesis of the changes within the small and medium sized pulmonary arteries seen in cases of pulmonary hypertension is not clear. Potential factors associated with this condition may be due to a genetically based hyperreactivity of pulmonary arteries[18], sheer stresses on the pulmonary arteries, injury to the pulmonary endothelium, or changes induced by toxins, drugs and infections.[6,11,14,19] Chronic changes within the pulmonary arteries due to increased flow have been associated with altered nitric oxide and endothelin responses.[4] Endothelin-1, a potent vasoconstrictor, has been associated with increased pulmonary flow in left-to-right shunts independent of pulmonary artery pressure.[4,17] Pulmonary arteries exposed to high flow and pressure also have been reported to have increased levels of VEGF, which suggests the ongoing process of tissue remodeling.[10,12]

**Contributor:** University of Tennessee College of Veterinary Medicine, Department of Pathobiology, Knoxville, TN 37996-4542
http://www.vet.utk.edu/departments/path/

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**CASE II – 07-0613 (AFIP 3066389).**

**Signalment**: An adult, female, German shepherd dog (*Canis familiaris*)

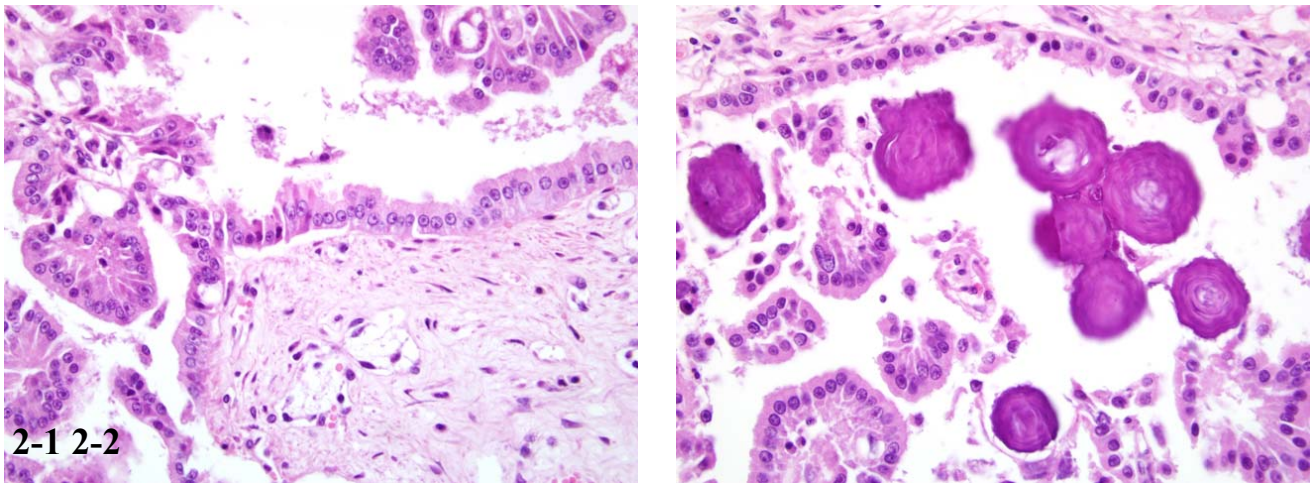
**History:** A 6-year-old female German shepherd dog was presented for a posterior ataxia and a bilateral quadriceps amyotrophy. At neurological examination, the posterior patellar reflex was bilaterally increased and the posterior proprioceptive reflexes were decreased. The dog was euthanized for humane reasons and a complete necropsy examination was undertaken.

**Gross Pathology:** At necropsy, a nonencapsulated, grayish granular mass was observed within the 4th ventricle. Nodular and multifocal intradural dull gray lesion with a granular cut surface was also observed on the ventral face of the brain stem scattering along the spinal cord. The nodules were firm, and had expansive growth without evidence of infiltration of the brain and spinal cord parenchyma. They compressed and displaced the spinal cord.

**Laboratory Results:** No significant bacterial pathogens were culture.

White blood cells count: 67 x $10^3$ cells/mL (leucocytosis)
Red blood cells count: 2,3 x $10^6$ cells/mL (anemia)
Hematocrit : 18%
MCH: 63 g/L
Reticulocyte count : 50 %

**Histopathologic Description:** Spinal cord cross and sagittal sections: At histopathological examination, the ventral subarachnoidal space of the spinal cord and the nerve roots were severely infiltrated by a multinodular, poorly-demarcated, partially encapsulated mass with a moderate cellularity. The tumor was composed of papillary structures supported by a delicate fibrovascular stroma **(Fig. 2-1)**. The neoplastic cells were cuboidal or columnar, measuring 15 to 20 µm with well-defined cytoplasmic borders. The cytoplasm was abundant and pale eosinophilic. The nucleus was round, basally located, euchromatic with coarse chromatin. The mitotic index




*2-1. Meninges, German Shepherd Dog. Neoplastic cell form fibrovascular papillary projections which are lined by a single row of cuboidal to low columnar epithelium. (HE 400X).*
*2-2. Meninges, German Shepherd Dog. Within neoplasm there are moderate numbers of deeply basophilic, round, often lamellated concretions (psammoma bodies). (HE 400X).*

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was 3 to 4 mitoses per high power field and was dependent on examined area. Atypia cellular was moderate to strong: anisokaryosis and anisocytosis, nuclear gigantism, prominent nucleoli and multinucleated cells. No embolus was found. Numerous psammoma bodies and foci of mineralization were observed and focal perivascular accumulation of lymphoid cells was noted **(Fig. 2-2)**.

**Contributor's Morphologic Diagnosis:** Spinal cord: Meningeal metastasis of choroid plexus carcinoma (meningeal carcinomatosis)

**Contributor's Comment**: Choroid plexus tumors are usually rare and benign tumors. They have been described in man, cattle, horses, goats, cats, mice and dogs. The average age of affected dogs is 6 years and male dogs are up to three times more commonly affected than females, but there is no breed predisposition. In human pathology, choroid plexus carcinoma occurs mainly in children under 3 years of age.

The fourth ventricle is the most common site for these tumors in man and dog. In our case, a primary mass was detected microscopically in the choroid plexus of the fourth ventricle. No significant lesion was detected at post mortem examination so the possibility of metastasis of another tumoral process was ruled out. The spinal cord tumor was multiple without embolus so the hypothesis of a meningeal carcinomatosis due to diffusion of the neoplastic cells through cerebrospinal pathways is highly probable. Concerning immunohistochemistry, it is reported that Pankeratin and CK AE1 positivity is observed in choroid plexus carcinomas with marked cell anaplasia, whereas CK AE3 is expressed by well-differentiated neoplastic cells.[1] Vimentin positivity is observed in a large number of neoplastic cells. EMA and S-100 give negative results in all cases of choroid plexus carcinoma.

**AFIP Diagnosis:** Meninges, spinal nerve root: Metastatic choroid plexus carcinoma, German shepherd dog (*Canis familiaris*), canine.

**Conference Comment**: While some have proposed including a category of choroid plexus papilloma with atypia,[4] two major forms of choroid plexus tumors are generally recognized: choroid plexus carcinoma and papilloma. Any form of anaplasia and/or metastasis, including metastasis of well-differentiated tumors within the ventricular system and along the neuraxis, is sufficient for a diagnosis of choroid plexus carcinoma.[3] Anaplastic features include nuclear atypia, loss of papillary architecture with transition to patternless cellular sheets, an increased mitotic index, and necrosis.[2,3]

Papillary ependymomas can be included in the differential diagnosis for choroid plexus tumors. On H&E, ependymomas contain pseudorosettes, occasionally true rosettes with cilia, and have a glial rather than a fibrovascular core.[2,3] Immunohistochemistry may be necessary to differentiate the two.

By immunohistochemistry performed at the AFIP, neo-

***Table adapted from Ribas et al.[4] and Koestner et al.[2]***

| Immunohistochemical stain | Ependymoma (Papillary) | Choroid plexus tumor |
|---|---|---|
| Cytokeratin Usu | ally negative | Positive |
| Vimentin Po | sitive | Positive |
| GFAP (glial fibrillary acidic protein) | Positive | Usually negative, but rarely positive |

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plastic epithelial cells in this tumor had positive cytoplasmic immunoreactivity to cytokeratin and GFAP. While most reported cases of canine choroid plexus tumor are negative for GFAP, at least one case in the literature was positive for GFAP. [1] GFAP positivity of some canine choroid plexus tumors is not surprising based on their histogenesis and the findings in human choroid plexus tumors. Human choroid plexus tumors are often positive for both epithelial markers and glial markers reflecting their hybrid nature. Ependymomas should be widely positive for GFAP and are generally negative for cytokeratin.[5]

**Contributor:** Department of Veterinary Pathology, Nantes Veterinary School, Atlanpôle-la Chantrerie, Nantes, France.

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**CASE III – 06-11733 (AFIP 3067218).**

**Signalment:** 10-month-old, castrated male, Newfoundland, *Canis familiaris,* canine.

**History:** The patient was presented to the referring veterinarian with a history of decreased appetite, cough, gagging and regurgitation not associated with eating. The mother and two littermates had died recently after showing similar clinical signs.

There was an episodic fever most apparent during morning and evening associated with an increase in his coughing and regurgitation episodes. The referring veterinarian sent out ANA, ACH receptor, and T4 titers. The ANA was positive at 1:50 and the other results are not available. Thoracic radiographs were taken and an initial diagnosis of megaesophagus was made. An endoscopy was performed and some degrees of esophageal and gastric mucosal scarring were detected. The dog was started by the referring veterinarian on antibiotics, antacids and gastric protectants and then transferred to the Foster Hospital for Small Animals at the Tufts University Cummings School of Veterinary Medicine.

On initial physical exam at Tufts the animal was depressed and gagging on palpation of his trachea. There were harsh lung sounds dorsally and bilaterally. Tho -

racic radiographs showed patchy interstitial to alveolar lung pattern in the right lung lobes and left cranial lung lobe, consistent with aspiration pneumonia. The initial therapy at Tufts included IV fluids, antibiotics and Vitamin E and Selenium. A presumptive diagnosis of polymyositis was made and due to the overall poor prognosis and rising expenses the owner elected euthanasia and an autopsy was performed. Muscle biopsies were submitted to the neuromuscular laboratory at UC Davis.

**Gross Pathology:** The retropharyngeal and mediastinal lymph nodes were enlarged. The esophageal mucosa and serosal were normal and there was no evidence of megaesophagus. The lung lobes were mostly (70%) dark red to brown heavy and wet.

**Laboratory Results:**
CBC: WNL.
Taurine:

- Plasma 19 nmol/l (normal values: 60-120)
- Whole blood: 212 nmol/l (normal values: 300-600)

UA: Specific gravity (1.017)
Toxoplasma and neospora titers – cancelled

**Histopathologic Description:** Esophagus (Submitted slides contain a full-thickness section of distal esophagus, and many include a portion of the gastric cardia): There is mild, multifocal hyperplasia of the stratified squamous epithelium. The muscularis externa is markedly thinned and distorted. Lymphocytes, epithelioid macrophages and occasional neutrophils infiltrate the outer longitudinal muscular layer. Fibroblasts dissect and efface the myofibers and the interstitium is expanded by immature, pale basophilic connective tissue stroma (endomysial fibrosis). Skeletal muscle fibers are markedly distorted and irregular with hyalinization, loss of striation, cytoplasmic pallor and occasional multiple large internalized nuclei. Few hypereosinophilic myocytes with pyknotic nuclei are also present.

**Contributor's Morphologic Diagnoses:** Esophagus: Severe, diffuse, chronic, lympho-histiocytic myositis with myocyte degeneration, necrosis and regeneration.

**Contributor's Comment:** The histological findings in this 11-month-old, Newfoundland dog are consistent with a polymyositis and the localization of the lesion (tongue, esophagus, larynx and pharynx) explain the clinical signs exhibited by this animal. Skeletal muscles from the limbs and trunk were unaffected. No bacterial, fungal or protozoal organisms were detected. In addition the histological diagnosis of polymyositis was confirmed by Dr. Diane Shelton at U.C. Davis. [ Immunohistochemical staining with staphylococcal protein A -HRP revealed sarcolemmal positive staining consistent with autoantibodies (staphylococcal protein A binds to the FC region of immunoglobulin heavy chains)]

Inflammatory myopathies are a group of disorders characterized by nonsuppurative inflammation of skeletal muscles. Polymyositis is an immune-mediated, generalized skeletal muscle disorder characterized by muscular weakness, muscular atrophy, elevated serum concentration of creatine kinase, abnormal electromyography, negative serologic tests for infectious disease and lymphocytic infiltrate.[4] Some forms of generalized myositis are associated with protozoal, rickettsial or bacterial infections.[1] In human medicine and in few veterinary medicine cases, inflammatory myopathies have been associated with malignant neoplasia.[2,6]

Some inflammatory myopathies can be localized to particular groups of muscles such as the masticatory muscles[15] and extraocular muscles.[3] Such particular distributions are likely related to molecular characteristics of particular muscle groups. Masticatory muscles myositis for example affects all muscles innervated by the mandibular branch of the trigeminal nerve (masseter, temporalis, pterygoids, tensor tympani and tensor veli palatine muscles) and is characterized by clinical signs such as jaw pain, inability to open the jaw and masticatory muscles atrophy. Masticatory muscles contain a distinctive muscle fiber, type 2M, which is biochemically and histocemically different from the muscle fibers contained within other skeletal muscles.[15] Serum antibody titer for type 2M fibers is negative in extraocular myositis. The targeting of specific muscles in the current case suggests that these muscles may be distinct in some way from other skeletal muscle in the body.

Inflammatory polymyositis has been most thoroughly reported in veterinary medicine in Collies, Shetland sheepdogs and Newfoundlands, and it seems to be related to a generalized immune-mediated disorder.[9] The association of inflammatory myositis with malignant neoplasia in dog has not been completely demonstrated, while it in human medicine it is commonly reported.[2]

**AFIP Diagnosis**: Esophagus: Myositis, lymphoplasmacytic, histiocytic, subacute to chronic, diffuse, moderate, with muscle degeneration, necrosis and regeneration, Newfoundland dog (*Canis familiaris*), canine **(Fig. 3-1 3-2, 3-3)**.

**Conference Comment:** Inflammatory myopathies can be divided into two broad categories based on whether an underlying cause can be identified. The idiopathic or presumably immune-mediated neuromuscular diseases

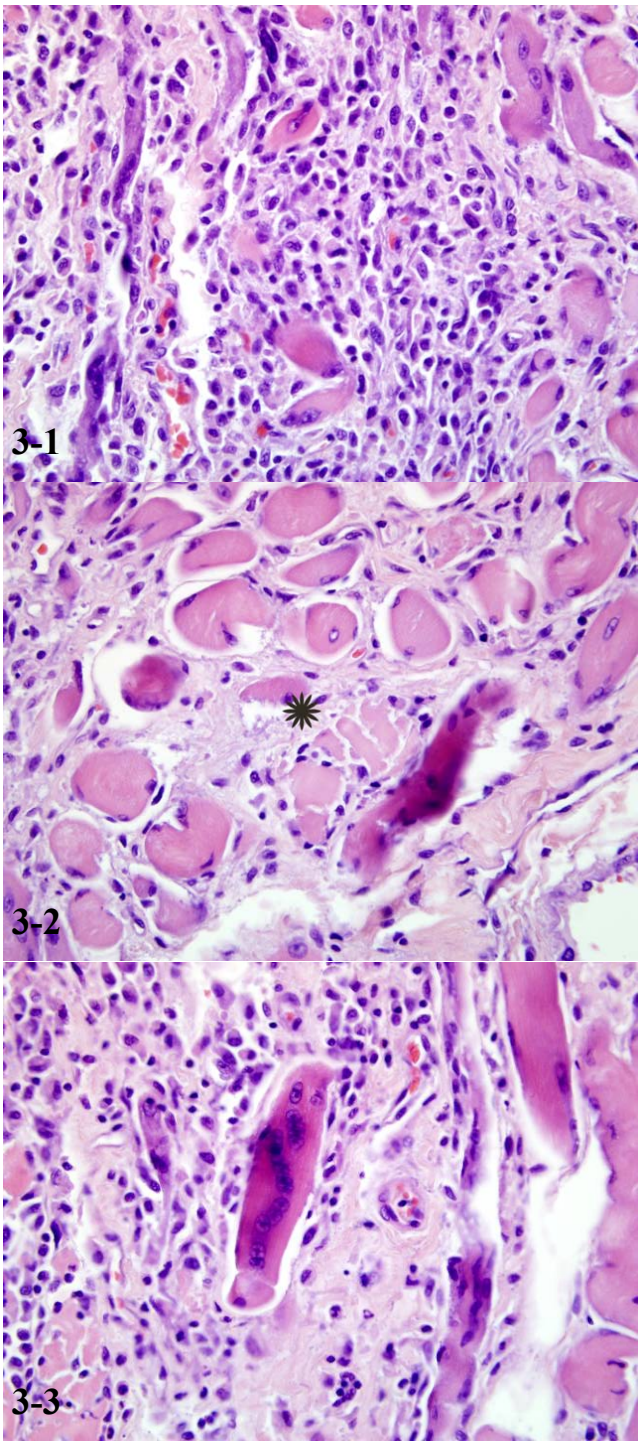
include polymyositis (PM), masticatory muscle myositis (MMM), extraocular myositis, and dermatomyositis.[13,15] Secondary inflammatory myopathies may include those secondary to infectious agents (*Neospora caninum*, *Toxoplasma gondii*, *Hepatozoon americanum*, *Clostridium chauvoei*, *Ehrlichia canis*), paraneoplastic diseases (thymoma), drug-induced myopathies (D-penicillamine, Cimetidine, Trimethoprim-sulfadiazine), or connective tissue diseases (systemic lupus erythematosus).[4,13]

Generally, the muscles affected in MMM are specific to the muscles of mastication and spare the extraocular, esophageal, and limb muscles. In addition to autoantibodies against type 2M fibers, autoantibodies against myositigen, a masticatory muscle variant of the myosin binding protein C family, has been identified in cases of MMM.[18] The cellular infiltrate in cases of MMM has some distinct differences between those seen in other types of inflammatory myopathies. In MMM, B-cells, dendritic cells, and macrophages are seen in greater numbers than T-cells, and the CD4+ T cells are seen in greater numbers than the CD8+ T cells.[14,16]

In polymyositis (PM), B cells are not a prominent feature, while CD8+ T cells are present in great numbers than CD4+ T cell. Both MHC class I and class II antigens are upregulated in cases of PM as well as MMM.[12,14,16] In the Boxer and Newfoundland breeds, a sarcolemma-specific autoantibody has been identified in some dogs with PM. In general, dogs with PM will not have autoantibodies against type 2 M fibers, although there have rare reports of on overlap syndrome in which dogs will have features of both PM and MMM.[4,15]

Extraocular myositis is an inflammatory condition restricted to the extraocular muscles; Golden retrievers may be more susceptible. Bilateral exophthalmos due to swelling of the extraocular muscles may be the only clinical sign, and may resemble the acute form of MMM.[3, 16]

Dermatomyositis is a breed-related (Collies, Shetland sheepdogs), autoimmune disorder of skeletal muscle,




*3-1. Esophagus, Newfoundland. Diffusely separating, surrounding and replacing myocytes are high numbers of lymphocytes, plasma cell and histiocytes. Within this area individual myocytes are often atrophied. (HE 400X).*
*3-2. Esophagus, Newfoundland. There is multifocal myocytes necrosis characterized by loss of cross striations and fragmented sarcoplasm (star). (HE 400X).*
*3-3. Esophagus, Newfoundland. There is multifocal myocyte regeneration characterized by myofibers with lightly basophilic sarcoplasm, multiple, centrally located, linearly arranged euchromatic nuclei with prominent nucleoli. (HE 400X).*

skin, and the vasculature.[5,10,11,16,17] A perifascicular pattern of muscle fiber atrophy is considered a characteristic component of this disease.[8,16] Cutaneous lesions are characterized by mild, perifollicular, mixed inflammation with follicular atrophy, follicular basal cell degeneration to the level of the isthmus, ulceration, crusting, smudging of the dermal collagen, and occasional vesiculations.[7,13]

**Contributor**: Section of Pathology, Department of Biomedical Sciences, Tufts University Cummings School of Veterinary Medicine, North Grafton, MA. http://www.tufts.edu/vet/

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**CASE IV - 05-9637 (AFIP 2986812).**

**Signalment:** A mixed breed (miniature schnauzer) dog, 12 years, spayed female

**History:** The dog was presented in 2003 with a growth in the ventral neck region (approximately 3cm diameter). The mass was excised at that time and in 2005 the mass had re-grown. Again the tumor was excised and a diagnosis similar to the 2003 evaluation was made.

**Gross Pathology:** A round mass, 2-2.5cm in diameter was attached to the left thyroid gland.

**Laboratory Results:** CBC and chemistries were all unremarkable except for slight elevation of ALP and ALT, both in the 300's. The animal had slightly elevated ionized calcium at 1.5. Total calcium was normal. Urinalysis was unremarkable. Thoracic and abdominal radiographs and abdominal ultrasound were unremarkable. No evidence of metastatic disease was found. Sections of the neoplasm were immunostained to confirm the biologic activity of the tumor.

**Histopathologic Description:** A soft tissue mass from

the ventral neck consists of a very cellular mass, a neuroendocrine neoplasm **(Fig. 4-1)**. The cells are in packets separated by a thin vascularized stroma. Peripheral to the mass are numerous satellite nodules with tumor invasion of the lymphatics. The lesion was immunohistochemically positive for thryocalcitonin and negative for thyroglobulin and parathormone.

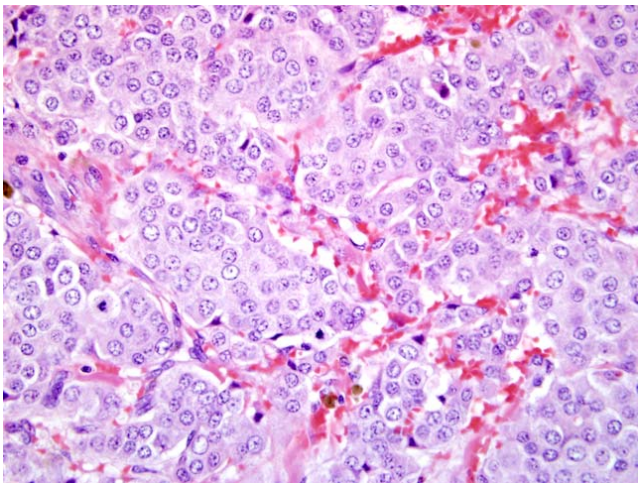
**Contributor's Morphologic Diagnosis:** Mass: Thyroid carcinoma parafollicular

**Contributor's Comment:** Incidence: The C-cell thyroid parafollicular cells are seen most frequently in adult cattle[2,11], aged horses [9] and infrequently in other domestic species.[12,22] As bulls age there is an increased incidence of neoplastic C-cells, especially where bulls are fed high calcium diets. [13] Multiple endocrine tumors have been associated with pheochromocytoma in bulls with C-cell tumors.[19] In the dog, a pheochromocytoma has been also associated with parathyroid chief cell hyperplasia.[15] In a histochemical study of 33 thyroid carcinomas in the dog, 36% were of C-cell original and 64% were from thyroid follicle cells.[4] The affect on the elevated calcium is uncertain. In adult bulls, various skeletal lesions have been associated with C-cell neoplasia.[20] In man, prominent bone lesions have not been reported as the result of excessive calcitonin.[14]

**AFIP Diagnosis**: Fibrovascular tissue, ventral neck (per contributor): C-cell (parafollicular) carcinoma, mixed breed dog (*Canis familiaris*), canine.

**Conference Comment**: In domestic animals, most thyroid neoplasms are thyroid follicular cell tumors or C-cell (also called parafollicular or medullary) tumors. These tumors can have similar (endocrine/neuroendocrine) histologic features, ie. packets and trabeculae of epithelioid cells supported by a fine fibrovascular stroma. While C-cell carcinomas may have pallisading of columnar cells along the periphery of the lobules, dense bands of connective tissue, and/or amyloid deposits, and thyroid follicular cell tumors usually have some follicular differentiation, immunohistochemistry may be needed to differentiate between thyroid follicular cell tumors and C-cell tumors. One study[4] suggested that C-cell tumors have been underdiagnosed when the diagnosis was based on histologic evaluation of H&E stained sections alone.

C-cell neoplasms exhibit positive cytoplasmic immunoreactivity for calcitonin and are negative for thyroglobulin. The sensitivity for thyroglobulin for thyroid carcinomas is 90.5% alone, but if it is combined with TTF-1, that sensitivity increases to 95.2%.[16] TTF-1, thryoid transcription factor, is expressed in the thyroid, brain, and lung during early embryogenesis, and the thyroid cells and bronchioloalveolar epithelial cells following birth. In the lung, it activates surfactant proteins and Clara cell secretory protein gene promoters.[1] In the thyroid gland, it activates many factors including thyroglobulin, thyroperoxidase, thyrotropin receptor, and thyroid peroxidase.[5,6,8,10,18] When positive, TTF-1 is diffusely located within the nucleus and never in the cytoplasm. In one study, approximately 50% of the C-cell neoplasms also stained positive for TTF-1, therefore it is not suitable to use as a single marker.[16]



*4-1. Thyroid gland, mixed breed dog. Neoplastic cells are polygonal with indistinct cell boarder moderate amounts of finely granular cytoplasm with round nucleoli, finely stippled chromatin, variably distinct nucleoli and arranged in nests and packets supported by a fine fibrovascular stroma. (HE 400X).*

C-cell tumors in bulls, often occur concurrently with bilateral pheochromocytomas and pituitary adenomas.[4] Multiple endocrine tumors are thought to arise due to a simultaneous neoplastic mutation of multiple endocrine cell populations of neural crest origin in the same individual.[3,23] In humans, multiple endocrinen neoplasia type 2 (MEN-2) occurs in an autosomal dominant pattern, and is classified into three clinical manifestations.[17] MEN-2A is characterized by the presence of a medullary thyroid carcinoma in addition to a pheochromocytoma and multiple tumors of the parathyroid gland.[7] MEN-2B consists of a medullary thyroid carcinoma, a pheochromocytoma, ganglioneuromatosis, and marfanoid habitus.[21] FMTC syndrome, is the third form of MEN-2 and is defined as the development of a medullary thyroid carcinoma and a low incidence of other clinical manifestations of either MEN-2A or MEN-2B.[7]

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