Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2017-2018

C o n f e r e n c e 19

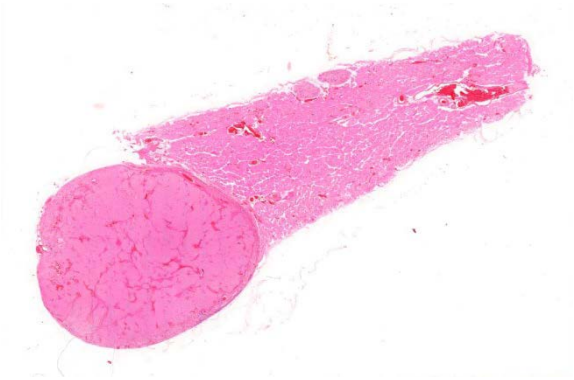
4 April 2018

Donald Meuten, DVM, PhD, DACVP (Anatomic and Clinical Pathology)

CASE I: P46/14 (JPC 4048933).

Signalment: 8-year-old, female, spayed, Bernese Mountain Dog (*Canis lupus familiaris*), canine.

History: 8-year old spayed Bernese mountain dog with hypercalcemia and elevated levels of parathyroid hormone. An enlarged parathyroid gland (9x13mm) and a slightly enlarged thyroid gland were found on the right side with ultrasound. The left parathyroid and thyroid gland were considered to be within normal variation. The right parathyroid and thyroid were removed with surgery.



Thyroid gland, dog. At one edge of the section, expanding the parathyroid gland, there is a 1.1cm round expansile neoplasm. (HE, 4X)

Gross Pathology: The parathyroid gland was markedly enlarged, had a hard texture and was firmly attached to the thyroid gland.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): see below

Before surgery

// RHA

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
S-Fosfat	0,7	mmol/L	0,8 1,9	KLAB
S-Kalcium	3,2	mmol/L	2,3 2,8	KLAB
S-Kreatinin	121	umol/L	46 115	KLAB

// RHA

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
S-Glukos		mmol/L		

// RHA

Bilddiagnostik

Buk ,

U-pH	8		6 7	KLAB
U-Densitet, profil	1,012	kg/l		KLAB
U-protein profil	0			KLAB
U-hemoglobin	0		0	KLAB
U-glukos	0		0	KLAB
U-aceton	0		0	KLAB
U-Leukocyter	0	/synfält	0 3	KLAB
U-Erytrocyter	0	/synfält	0 3	KLAB
U-Cylindrar	0	/synfält	0 2	KLAB
U-Kristaller	0	/synfält		KLAB
U-Epitel	0	/synfält		KLAB

// RHA

Lab

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
Provtagningsavgift blod	-			
ABL90 joniserat Ca	-			
iCa2+	1,56		1,29 1,46	iåm

// IÅM

Lab

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
C-reaktivt protein CRP (hund)	<5		< 5	KLAB
S-Albumin	31	g/L	27 37	KLAB
S-Protein	66	g/L	56 75	KLAB
S-Kalcium	3,1	mmol/L	2,3 2,8	KLAB
S-Fosfat	0,8	mmol/L	0,8 1,9	KLAB

// EJI

Analys:	Värde	Enhet	Referensvärde	Sign

ENDOCRINOLOGY

Parathyroid Hormone * 144 pg/ml 20-65
Canine reference range = 20 - 65 pg/mL

PTH related protein (PTHrP) * 1.2 pmol/l <0.5
Ref. Range Note: >1.0 suggestive of malignancy

EDTA plasma sample received at Lab frozen 28th January

Authorised By : Ms Helen Evans BSc (Hons)
Laboratory Manager

Incomplete Tests : None
Test Codes : PTHR

AFTER SURGURY

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
S-Kalcium	2,6	mmol/L	2,3 2,8	KLAB
S-Kreatinin	115	umol/L	46 115	KLAB
S-Urea	4,3	mmol/L	2,5 8,8	KLAB
S-Fosfat	1,1	mmol/L	0,8 1,9	KLAB

// EJI

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
Provtagningsavgift blod				
ABL90 blodgaser/syrabas				
pH	7,468		7,33 7,46	ebo
kl.13.30				
HCO3-	23,0		22,2 - 27,2	ebo
pCO2	30,0		31,8 54	ebo
pO2	42,1		26,4 66,8	ebo
sO2	85,2		50 97,9	ebo
Htk	57,9		40,7 67,1	ebo
Hb	189		133 219	ebo
Na+	147		146 152	ebo
K+	4,4		3,6 4,8	ebo
Cl-	115		112 118	ebo
Ca2+	1,28		1,29 1,46	ebo

Glu	4,8		3,8 5,8	ebo
Lakt	1,2		0,8 2,2	ebo
BE	-2,0		-2,5 4,9	ebo
Aniongap	10,7		3,8 11	ebo

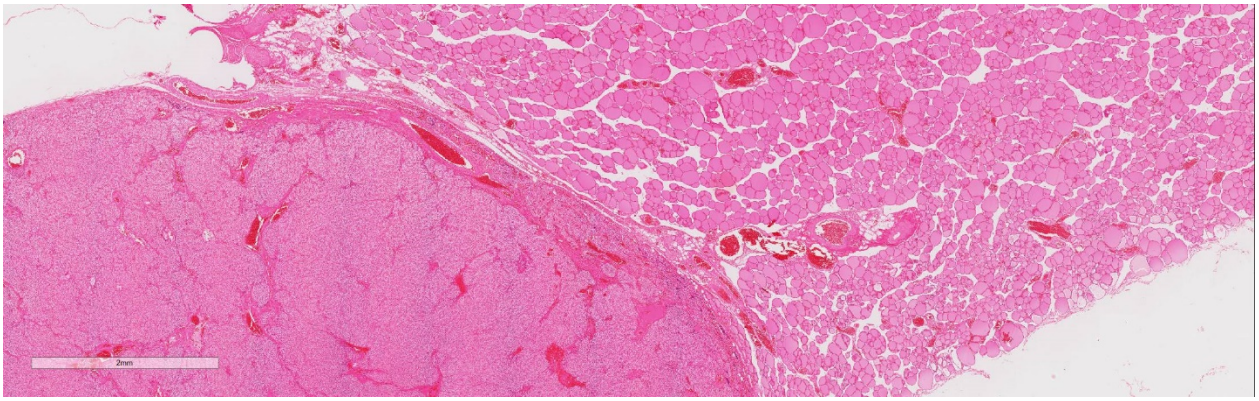
// EJI

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
S-Kalcium	2,7	mmol/L		SE
S-Kreatinin	122	umol/L		SE

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
Provtagningsavgift blod				
Tyreoidea pkt hd f-T4, TT4, TS				
Fritt T4 i paket	9,3	pmol/L		KA
Totalt T4 i paket	24	nmol/L		KA
TSH i paket	36	mU/L		KA

// LLE

Analys:	Värde	Enhet	Referensvärde	Sign
Utlåtande				
Provtagningsavgift blod	*			KLD
ABL90 joniserat Ca	*			KLD
iCa2+	1,37		1,29 1,46	KLD



Thyroid gland, dog. The border of neoplasm forms compresses the adjacent follicles and the advancing front forms a compression capsule from pre-existent stroma. (HE, 9X)

Microscopic Description: Adjacent to the thyroid gland is a large, well circumscribed, encapsulated expansive nodular neoplasia. The neoplasm mildly compresses the adjacent thyroid and focally neoplastic cells infiltrate the surrounding fibrous capsule. The neoplasm shows sheets of densely packed round cells (principally "chief" cells) and a moderate stroma consisting of thin fibrovascular tissue. Multifocally in the neoplasm are thicker bands of fibrovascular tissue and adjacent to these the neoplastic cells are arranged in a slight trabecular pattern with cords of cells palisading around thin fibrovascular septa. Scattered within the fibrous tissue are mononucleated cells with intracytoplasmic golden brown clumped pigment. The neoplastic cells reveal a mild pleomorphism with mild anisokaryosis and mild anisocytosis. The cells have a round nucleus, scant often vacuolated cytoplasm and indistinct cell borders. Mitotic index is low (5 mitoses/HPA) with presence of few atypical mitoses. Multifocally in the periphery of the neoplasm are groups of cells with hyperchromatic nuclei and no discernable cytoplasm believed to represent remnants of active dark principal cells. Additional parathyroid tissues are present in the periphery of the thyroid gland.

Contributor's Morphologic Diagnosis: Parathyroid gland, parathyroid carcinoma

Contributor's Comment: Parathyroid carcinomas are uncommon in domestic animals but have been observed in dogs and occasionally in cats, the etiology remains unknown. Among dogs, the tumor occurs most commonly in older animals.[1,7] The tumor arises from parenchymal chief cells resulting in unregulated secretion of parathyroid hormone that cause hyper-calcemia. The main differential diagnoses are the more common parathyroid adenoma and parathyroid hyperplasia. Anaplastic thyroid neoplasia and more rarely metastases of renal cell carcinoma should also be excluded.[1,4,5,8]

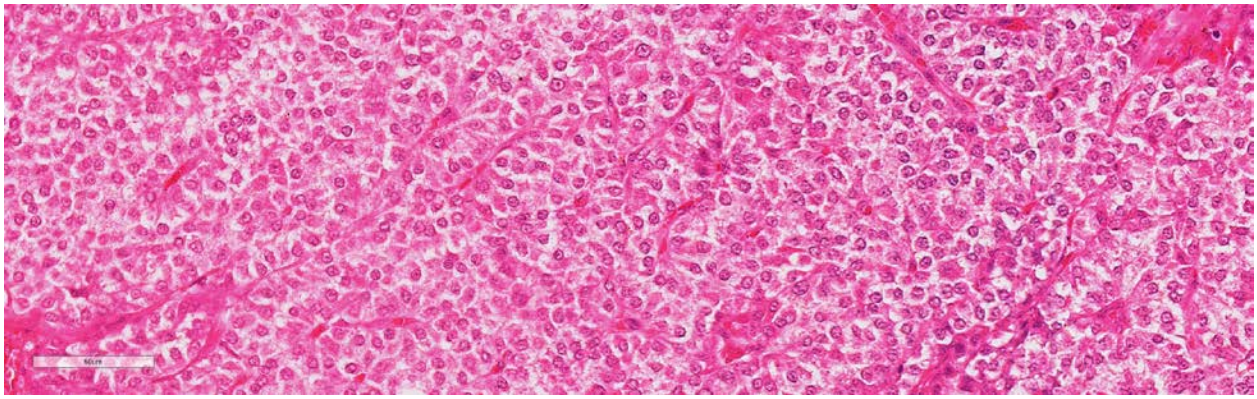
Clinical symptoms are due to hypercalcemia and include weakness, lethargy, polyuria, polydipsia and gastrointestinal disorders.[2,7,9] The most common symptom in dogs with parathyroid carcinoma appear to be weakness while in primary hyper-parathyroidism due to hyperplasia or adenoma polyuria and polydipsia seems to be more prone.[7] However it is difficult to distinguish between benign and malignant etiology since the clinical symptoms are similar. Most deaths related to parathyroid carcinoma are caused by hypercalcemia.[4]

Parathyroid carcinoma is not only a clinically challenging diagnosis but is also a difficult histopathological diagnosis since an overlap exists between pathologic features of parathyroid adenomas and carcinomas. Grossly, parathyroid carcinomas are larger than adenomas; the tumor is characteristically hard and greyish in appearance and is seemingly lacking surrounding fatty tissue more characteristic of adenoma. Histologically, parathyroid carcinoma commonly invades its surrounding capsule and adjacent structures. In carcinomas, there are usually greater degrees of cellular pleomorphism than in adenomas with more frequent mitotic figures and atypical mitoses. Since mitotic figures will sometimes be encountered in parathyroid adenomas, their presence alone is not be pathognomonic of carcinoma. Moreover, in carcinomas the chief cells form a trabecular pattern with thick fibrous bands and microscopic evidence of capsular and vascular invasion.[1,2,4,5,8] Carcinomas may metastasize to regional lymph node and lung but metastases are uncommon and usually occur late in the course of the disease.[2]

Surgery remains the primary management in treatment of parathyroid carcinoma. Neoplastic parathyroid tissue, both benign and malignant, is known to easily reimplant, to establish a new blood supply and marginal surgical excision is adequate for treatment.[2,4] Long term prognosis in dogs after surgery is often good.[7]

JPC Diagnosis: Parathyroid gland: Parathyroid adenoma, Bernese mountain dog (*Canis lupus familiaris*), canine.

Conference Comment: Both parathyroid adenomas and carcinomas can secrete parathyroid hormone (PTH) resulting in primary hyperparathyroidism. PTH functions to regulate ionized calcium in the blood in the following ways: (1) promoting excretion of phosphorus and retention of calcium in the renal distal convoluted tubules, (2) activation of osteocytic and osteoclastic bone resorption, and (3) retention of calcium in the intestines. Bony lesions are often most prominent in the bones of the maxilla and mandible of horses resulting in a condition known as “bran disease” or fibrous osteodystrophy where there is concurrent osteolysis and replacement with fibrous connective tissue. However, bone lesions are often more pronounced in secondary hyperparathyroidism, due to renal failure or nutritional imbalance.[6]



Thyroid gland. A monomorphic population of neoplastic cells is arranged in nests and packets with indistinct cell borders and a moderate amount of finely granular eosinophilic cytoplasm. Mitotic figures are rare. (HE, 335X)

Parathyroid gland adenomas are much more common than carcinomas in domestic animals. Certain breeds have familial tendencies, like Keeshond dogs, who are approximately fifty times more likely to develop parathyroid adenomas than other dog breeds due to an autosomal dominant trait. Microscopically, adenomas are composed of chief cells that are subdivided into smaller groups by a fine fibrovascular stroma. Chief cells can take one of two morphologies: (1) small amounts of lightly eosinophilic cytoplasm, or (2) large amounts of vacuolated, clear cytoplasm ("water clear cells"). The amount of cytoplasm (i.e. the morphology) is suggestive of the level of PTH secretion. More cytoplasm suggests more PTH synthesis and secretion.[6]

Chief cell hyperplasia can cause elevated PTH, but these lesions are often multifocal[6] and not one large compressive mass as this case.

As mentioned by the contributor above, parathyroid carcinomas are often larger than adenomas and characterized by invasion into the capsule, adjacent thyroid gland or other tissues, and veins or lymphatics. Microscopically, chief cells are often more irregularly arranged, pleomorphic, and have higher mitotic rates. In cats, chief cell carcinomas are often multinodular with numerous cysts lined by attenuated chief cells.[6]

Attendees discussed whether this lesion is a neoplasm or parathyroid hyperplasia. Based on the number of mitotic figures and size, it is more consistent with a neoplasm. Additionally, the neoplasm, though quite large and compressive, does not appear to be invasive. Therefore, we respectfully disagree with the contributor and prefer the diagnosis of adenoma rather than a carcinoma, although this generated much discussion. There was normal parathyroid gland that was compressed against the capsule adjacent to the neoplasm which some attendees thought might have been neoplastic invasion, but the general consensus was that it was normal parathyroid gland based on a slight difference in cellular organization and a thin septum between it and the neoplasm. Participants found it curious that the interior parathyroid gland is not atrophied, which would be expected with a PTH-producing adenoma and makes the laboratory findings perplexing (elevated pre-operative PTH with resolution of calcium and phosphorus levels after surgery).

In the normal parathyroid gland, attendees described aggregates of basophilic nuclei with cells that appeared to be fused. Some thought them to be lymphocytes, but the moderator properly identified those cells as normal cells which appear fused due to fixation artifact. The moderator explained that those cells had initially been identified as syncytial cells due to the fused plasma membranes identified ultrastructurally.[3] However, a few years later it was discovered that there are several parathyroid cell variants that occur secondary to immersion fixation.[10]

Finally, the moderator commented about clinical implications of measuring peptide hormones such as measuring PTH and calcium in surgery after the parathyroid tumor is removed but before the surgery is complete. These peptide hormones can change within minutes and return to normal. If this doesn't happen, the surgeon can check the contralateral gland for more tumors.

Contributing Institution:
Department of Biomedical Sciences and Veterinary Public Health, Section of Pathology, SLU (Swedish University of Agricultural Sciences)

http://www.slu.se/en/departments/biomedical-sciences-veterinary-public-health/

References:

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CASE II: 3855-16 (JPC 4101305).

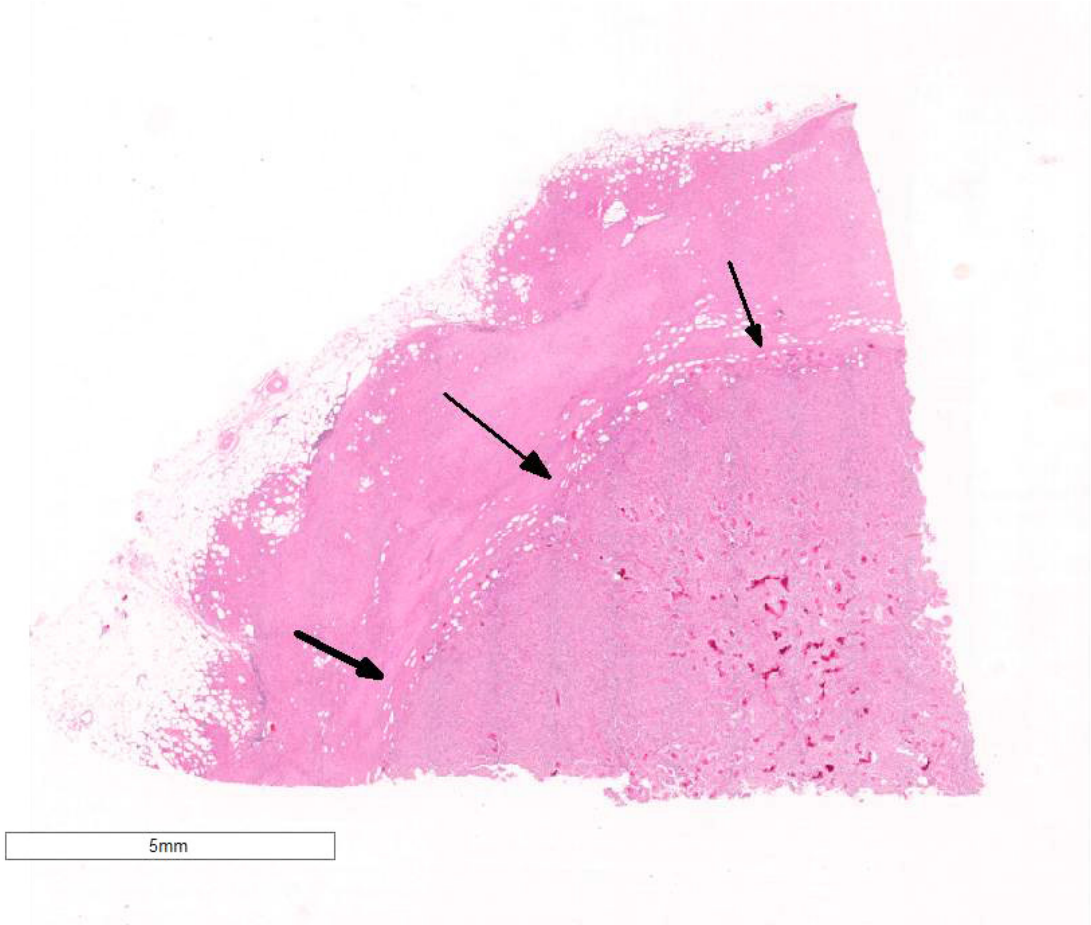
Signalment: 13-year-old female spayed Australian shepherd (*Canis familiaris*), canine.

History: This dog had a soft tissue mass on the dorsal left chest wall. The mass was deep and attached to chest wall muscles and invaded into adjacent fat. The surgeon dissected around mass and removed muscle where it was attached.**Gross Pathology:** Mass measured 5 x 4 x 3 cm

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): None provided.

Microscopic Description:

A 5 x 4 x 3 cm subcutaneous mass from behind the left shoulder blade is examined in four sections representing a cross section and lateral margins. The specimen has two distinct masses with a line of demarcation at their collision point. The peripheral mass is densely cellular, poorly circumscribed, and unencapsulated and is infiltrating into the adjacent subcutaneous adipose tissue. The mass consists of spindle-shaped cells arranged in bundles, streams, storiform patterns and whorls accompanied by collagen; the collagenous stroma varies from delicate to thick bands, in different regions of the tumor. The neoplastic cells are medium-sized with indistinct cellular margins and small amounts of fibrillar eosinophilic cytoplasm which blends with the stroma. The nuclei are medium-sized and oval with stippled chromatin and 1-5 nucleoli. Eleven mitotic figures are seen in ten high powered fields including a few atypical mitotic



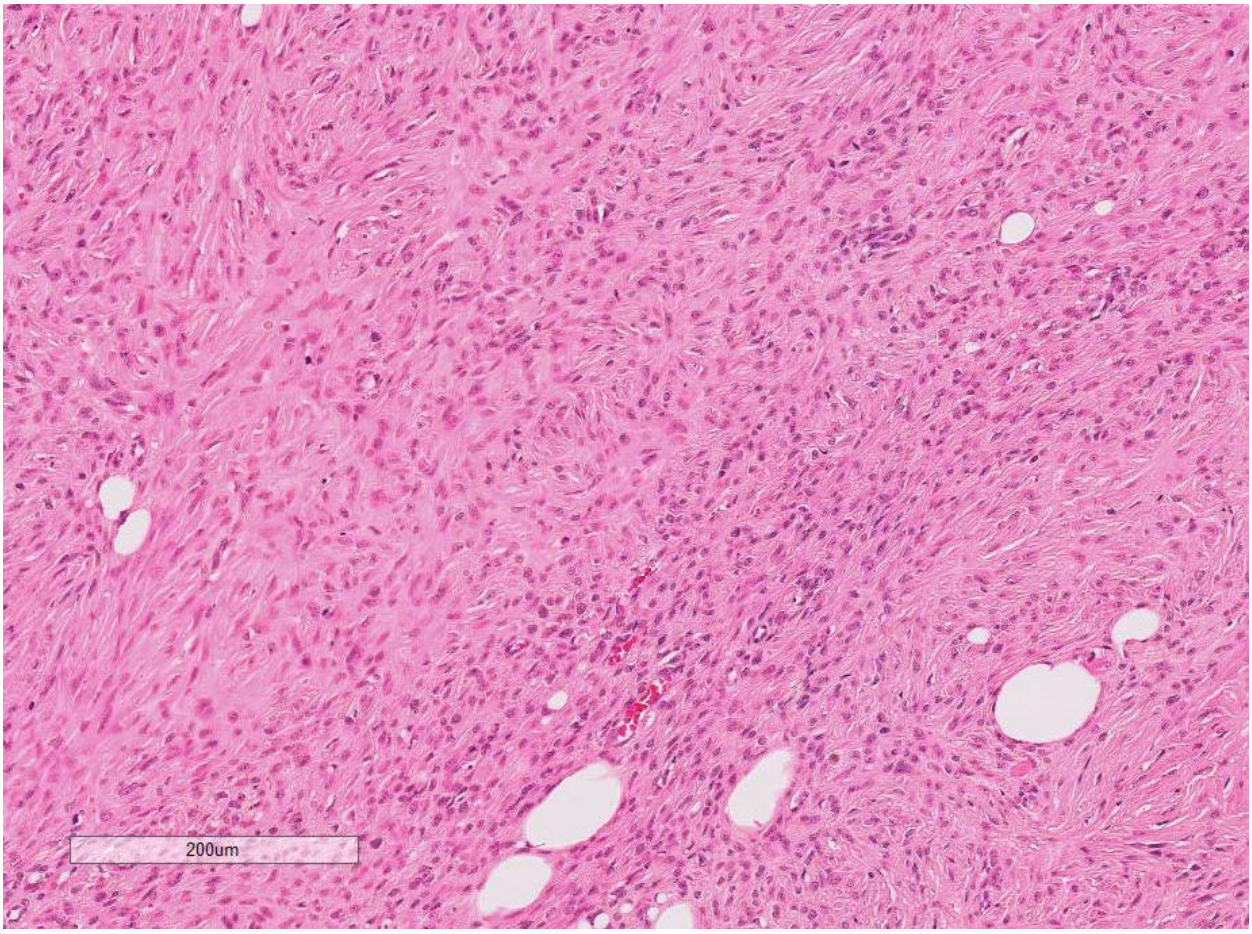
Soft tissue, chest wall: A single mass composed of two independent neoplasms is separated by a distinct border (arrows). (He, 5X)

figures. The central mass is densely cellular, circumscribed, unencapsulated, and slightly compresses the surrounding malignant peripheral nerve sheath tumor. The mass consists of plump spindle-shaped cells arranged in short streams and sheets accompanied by osteoid matrix. The neoplastic cells are medium to large with distinct cellular margins and moderate to large amounts of finely granular to fibrillar eosinophilic cytoplasm. The nuclei are large and oval with vesicular chromatin and 1-5 nucleoli. Thirty-two mitotic figures are seen in ten high powered fields, including a few atypical mitotic figures. The mass has moderate anisocytosis and anisokaryosis with rounded multinucleated giant cells occasionally scattered throughout it. The mass touches the deep and lateral margins.

Contributor's Morphologic Diagnosis:
Malignant peripheral nerve sheath tumor and osteosarcoma – collision tumor

Contributor's Comment: This neoplastic mass has a very unique histological appearance where the outer part has differentiated into a malignant peripheral nerve sheath tumor and the inner part has differentiated into an osteosarcoma. As there is a distinct junction between the two masses, this neoplasm was classified as a collision tumor.

Collision tumors are the result of two tumors in the same anatomic site which abut one



Soft tissue, chest wall: The first tumor (at upper left of the ubgross section,) is composed of moderate numbers of spindled cells forming tight bundles (storiform pattern). (HE, 120X.)

another but have a distinct demarcation between the two. Collision tumors are rare in domestic animals. Compared to collision tumors, biphasic or mixed tumors exist in which there are two intermixing phenotypically distinct populations of neoplastic cells. Reports of collision tumors involving melanomas are common.[3,6,8] Additionally, mixed Sertoli-seminoma tumors in the testes of dogs comprised nearly seven percent of all tumors in one study.[7] These collision and mixed tumors present a diagnostic dilemma as to how they arise, particularly if the tissue of origin is embryologically different.

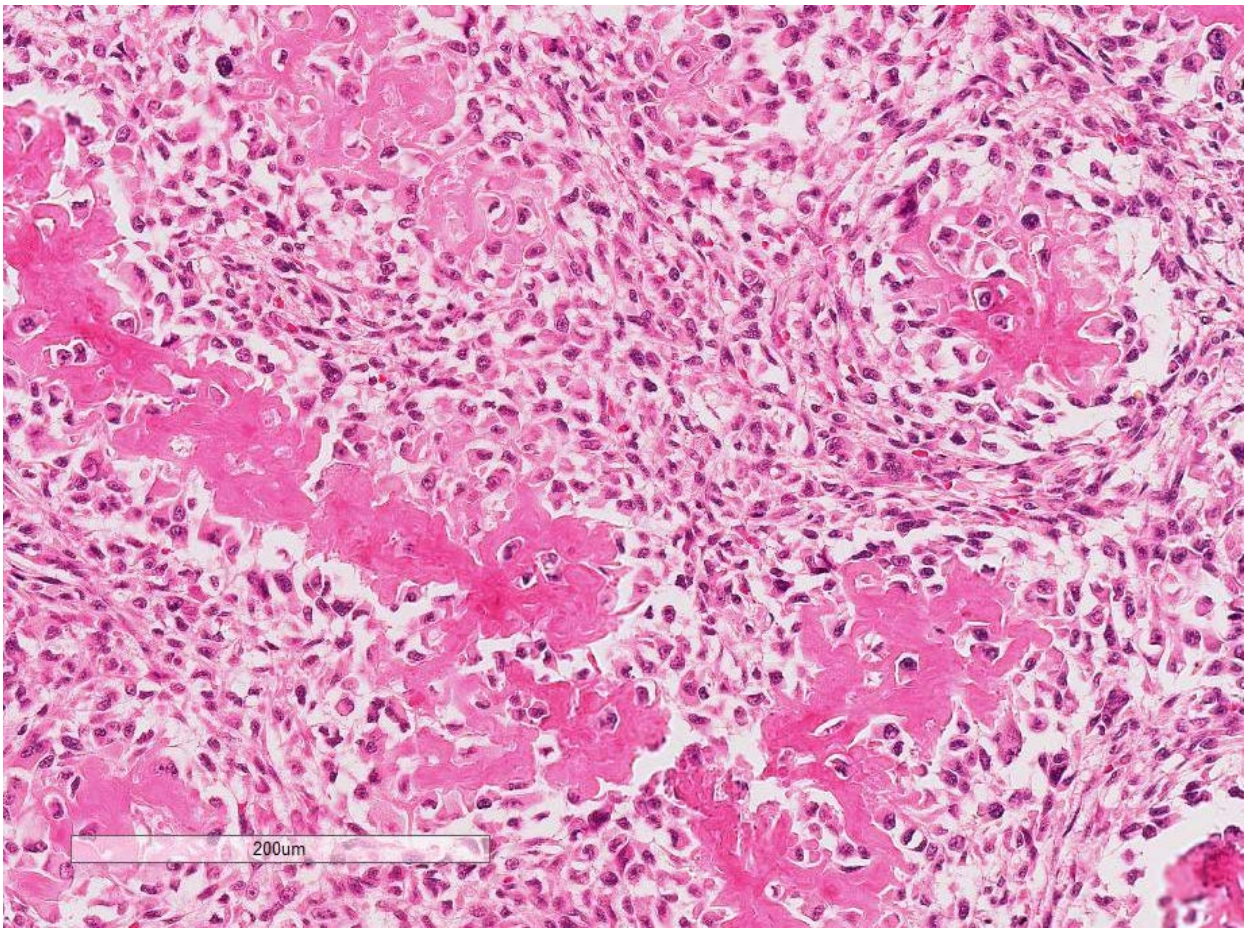
It is uncertain if this case represents a mass with growth of each neoplasm de novo, resulting in a collision of the two tumors or if there was metaplasia leading to development of a second tumor with characteristics of malignancy. Peripheral nerve sheath tumors are a heterogeneous group of tumors and their classification is confusing.[5] As the various classifications imply, there may be mesenchymal origin of these tumors that may undergo metaplasia. An example of cartilaginous differentiation exists.[5] It is feasible osseous metaplasia may, too, occur and develop into what appears to be a collision tumor.

JPC Diagnosis: 1. Fibrovascular tissue: Sarcoma (favor peripheral nerve sheath tumor), Australian shepherd (*Canis familiaris*), canine.
2. Fibrovascular tissue: Osteosarcoma.

Conference Comment: There have been several collision tumors reported in the veterinary literature within the last five years, including: malignant trichoblastoma/melanoma in a rabbit,[2] oral squamous cell carcinoma/malignant melanoma in a dog,[8] uterine adenocarcinoma/leiomyosarcoma in a goat,[1] perianal gland carcinoma/hemangiosarcoma in a dog,[9] and fibrosarcoma/mast cell tumor in a dog.[9] In most cases of collision tumors, the authors postulate that one tumor is primary and a second separate tumor occurs due to chronic inflammation, repetitive mitotic stimulation, and eventual neoplastic transformation of various local cell types. This differentiates collision tumors from mixed tumors, which are single tumors that include a mixture of different neoplastic cell types.

Collision tumors are also recognized in humans where much research is being done regarding their genetic profiles. For instance, it has been shown that intracranial collision tumors are composed of two distinct components. In the case of a combined meningioma and oligodendroglioma, there is deletion of chromosome 22q and 19q in both tumors initiating neoplastic transformation of both cell types.[4]

Attendees discussed the use of cytology with ALP staining for rapid diagnosis of



Soft tissue, chest wall. The second tumor (lower right of the Subgross image) is composed of plump active osteoblasts creating large amounts of osteoid. (HE, 155X)

osteosarcoma during surgery, remarking that sometimes biopsies can resemble reactive bone, especially if the sample is obtained from the periphery of the neoplasm. Additionally, participants discussed the special stains utilized in this case, including S-100, which exhibited strong, intra-cytoplasmic immunoreactivity for the spindle cell population of the sarcoma.

Contributing Institution:
Veterinary Diagnostic Center
School of Veterinary Medicine and Biomedical Sciences
University of Nebraska-Lincoln
http://vbms.unl.edu/nvdls

References:

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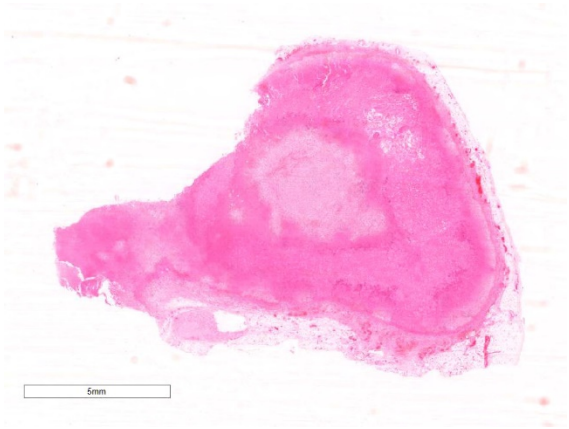
CASE III: W1161-16 (JPC 4102120).

Signalment: 15-year-old, male, neutered, Saluki (*Canis familiaris*), canine.

History: The dog had been previously diagnosed with hyperadrenocorticism based on low-dose dexamethasone suppression test, and treatment with trilostane was initiated. The dog was transported a long distance by plane and subsequently became in appetent. The animal was found collapsed in a kennel and taken to the University of Melbourne



Adrenal gland, dog: The entire adrenal cortex and large areas of the medulla are effaced by necrosis and hemorrhage. Israel, http://www.weizmann.ac.il/vet/)

veterinary referral service. At admission, the animal was recumbent and obtunded, with normal cranial nerve assessment. The dog was markedly tachycardic (180bpm) with a grade 1/6 left sided systolic heart murmur; an ECG revealed intermittent supraventricular tachycardia and occasional 2nd degree heart block. Body temperature was 39.8 ºC. Biochemistry, hematology and urinalysis results are presented below. The owner elected for the dog's euthanasia following consultation.

Gross Pathology: The liver was enlarged with rounded lobe margins and mottled red-brown coloration. The parenchyma was faintly nodular in structure and very friable. Within both adrenals there were multiple poorly-defined, variably sized, tan to beige colored soft tissue nodules, and multifocally within the adrenal parenchyma there were regions of dark red to black discoloration. The renal surface was irregularly indented, and underlying the indented areas there were wedge-shaped foci of parenchymal pallor extending through the cortex into the medulla.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): see below

Haematology	**Value**	**Canine Ref Values**
PCV %	**66**	37-55
RBC ($x10^{12}$/L)	**10.13**	5.65-8.87
Hb g/dL	**24.9**	8-12
MCV (fL)	64.9	61.6-73.5
MCH (pg)	23.2	21.2-25.9
MCHC (g/dL)	35.9	32.0-37.9
Neut ($x10^9$/L)	8.53	2.95-11.64
Lymph ($x10^9$/L)	1.29	1.05-5.10
Mono ($x10^9$/L)	0.42	0.16-1.12
Eosino ($x10^9$/L)	0.6	0.06-1.23
Baso ($x10^9$/L)	0.01	0.0-0.1
Platelet (K/µL)	325	148-484
PT	16	14-19
aPTT	88	75-105

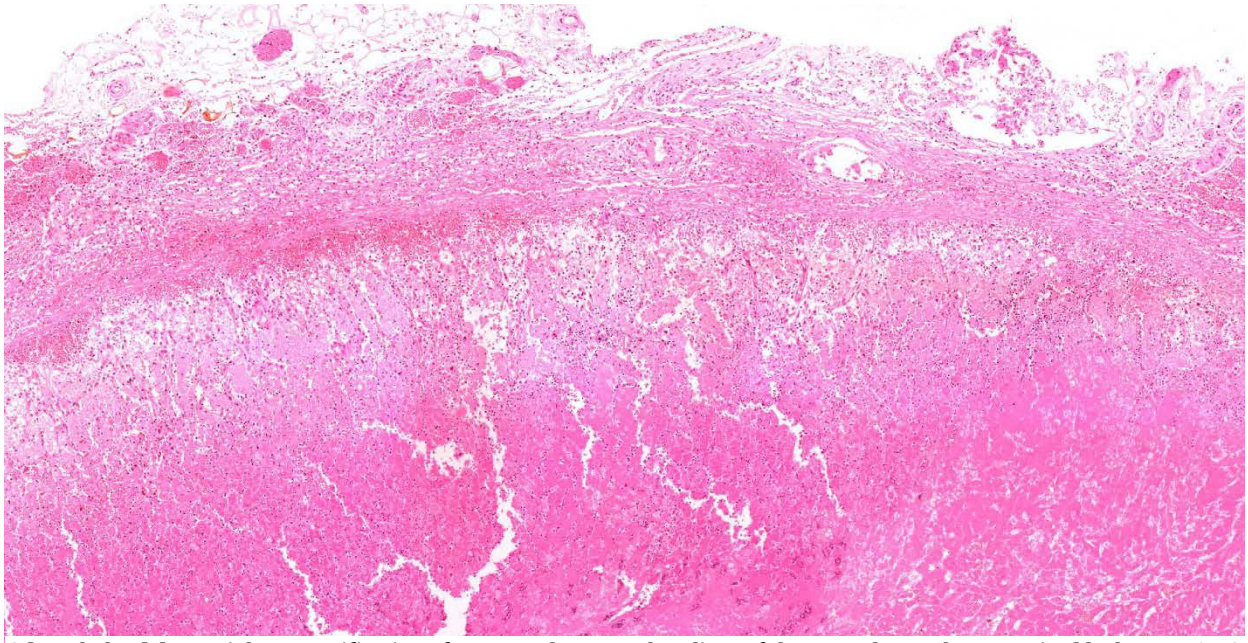
Biochemistry		
Urea (mmol/L)	**26.9**	2.5-9.6
Crea (µmol/L)	**460**	44-159
Phos (mmol/L)	**2.85**	0.81-2.2
TP (g/L)	61	52-82
Albumin (g/L)	29	22-39
Globulin (g/L)	32	25-45
ALT (U/L)	**239**	10-125
ALKP (U/L)	88	23-212
GGT (U/L)	0	0-11
T Bil (µmol/L)	6	0-15
Chol (mmol/L)	5.48	2.84-8.26
Amylase (U/L)	1485	500-1500

Lipase (U/L)	422	200-1800
Glu (mmol/L)	4.6	3.3-6.1
Lactate (mmol/L)	1.3	<2.0
K^+ (mmol/L)	**5.9**	3.6 – 5.8
Na^+ (mmol/L)	**140**	145 – 158
Ca^{2+} (mmol/L)	2.42	1.98-3.00
Cl^- (mmol/L)	115	105 – 122

Blood gases		
FiO2 %	.21	
A or V	V	V
pH	7.314	7.405
pCO2 mmHg	25.2	36.6
pO2 mmHg	34.5	52
HCO3 mEq/L	12.4	22
Anion Gap mmol/L	17.7	<24

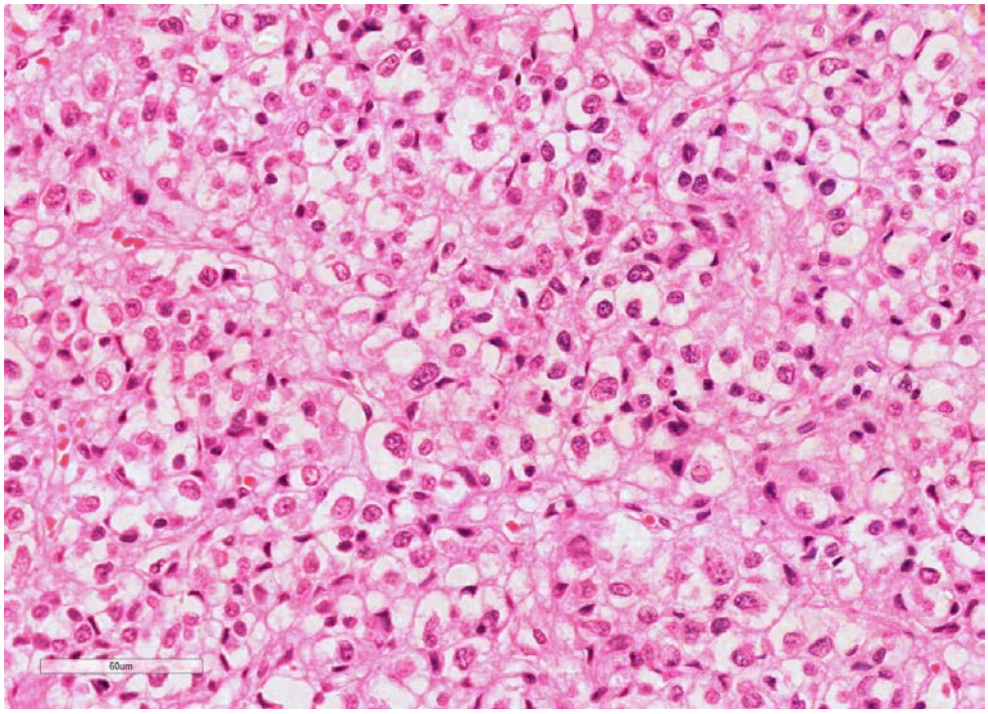
Urinalysis: USG 1.018, pH 6, trace protein. Rare casts and no bacteria noted on urine sediment exam.
LDDST: Cortisol 228 nmol/L at 0h (28-150 nmol/L), 128 nmol/L at 4h (<30 nmol/L), and 220 nmol/L at 8h (<30 nmol/L). (References in parenthesis)

Microscopic Description: Diffusely throughout the adrenal cortex there is loss of cellular detail, eosinophilic parenchymal homogeneity, and effacement of normal tissue architecture (necrosis). Multifocally



Adrenal gland dog. Higher magnification of cortex. The stromal outlines of the zona glomerulosa remain (black arrows). A line of hemorrhage, delineates them from the overlying edematous and hemorrhagic capsule, and the zona fasciculata and glomerulosa at bottom, are diffusely necrotic and largely effaced by hemorrhage. (HE, 69X)

within the affected areas there are deposits of lacy basophilic material (chromatin strands) and cellular debris which sometimes displays fine acicular clefting (cholesterol deposits), and there are also large regions that are suffused by extravasated erythrocytes (hemorrhage). Cortical cells in residual viable areas are poorly cohesive and are often swollen with cytoplasmic clearing (ballooning degeneration). There is relative sparing of the adrenal medullary structure, but the vasculature is moderately engorged and chromaffin cells display cytoplasmic eosinophilia (not present in all sections).



Adrenal gland dog. The majority of the adrenal medulla remains viable. (HE, 373X)

Surrounding the areas of necrosis, there is a marked infiltrate of neutrophils (predominantly degenerate) and macrophages, which extends beyond the capsule, and there is also a poorly organized population of fibroblasts within early granulation tissue. The connective tissue surrounding the adrenal is expanded and rarefied (edematous) with engorged vessels, multifocal hemorrhage and deposits of lacy eosinophilic material (fibrin).

Contributor's Morphologic Diagnosis:
Adrenal: Adrenocortical necrosis, severe, bilaterally diffuse, subacute

Contributor's Comment: Adrenal necrosis is infrequently identified in domestic species, with foci of necrosis identified in 1.8% of cats (n=159) and 3.0% of dogs (n=101) in a recent survey.[5] The necrosis in this case was attributed to an idiosyncratic response to trilostane therapy, resulting in secondary adrenocortical insufficiency and Addisonian crisis. Trilostane is commonly used for medical treatment of canine hyperadrenocorticism, and has superseded op'DDD as the drug of choice for control of this condition. It is a steroid analogue that reversibly inhibits adrenal steroidogenesis through blockade of 3β-hydroxysteroid dehydrogenase, thereby preventing the conversion of 3β-hydroxysteroids (pregenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone) to 3-ketosteroids (progesterone, 17-hydroxyprogesterone, and androstenedione).[10] Administration inhibits both mineralocorticoid and glucocorticoid synthesis, and sex hormone synthesis may also be impaired, although typically to a lesser degree. The metabolism of trilostane

has not been examined in detail in dogs, but in rats the drug is partially converted to ketotrilostane by the liver before being excreted fecally, while urinary excretion predominates in monkeys.[9]

There are multiple published reports of adrenal necrosis in dogs associated with trilostane administration.[2,11,12] Reutsch *et. al.* identified adrenal necrosis in five of seven dogs treated with trilostane for hyper-adrenocorticism.[12] This side-effect is not readily explained by the known effects of trilostane within the adrenal gland, and it has been proposed that the adrenal necrosis observed during trilostane therapy may reflect excessive secretion of adreno-corticotropic hormone (ACTH), rather than direct effects of the drug or its metabolites. This hypothesis is supported by trials demonstrating the development of adreno-cortical hemorrhage and vacuolization in rats treated with ACTH, whereas treatment with trilostane alone produced no histological lesions.[1] Moreover, adrenal hemorrhage has been observed clinically in humans receiving exogenous ACTH therapy.[7] The exact role of trilostane in the pathogenesis of adreno-cortical degeneration remains uncertain; however, it is possible that trilostane may promote hypersecretion of ACTH, or alternatively sensitizes adrenocortical cells to the toxic effects of ACTH. In the present case, we speculate that the stress of the flight prior to presentation may have precipitated excessive ACTH secretion and development of subsequent adrenal necrosis.

There are a large range of other chemicals capable of causing adrenal toxicity, as indicated in the table 1. The adrenal cortex is relatively susceptible to toxic effects due to its well-developed and highly permeable blood supply, its robust lipid metabolic pathways with strong uptake of lipophilic substances, and its abundance of cytochrome P450 enzymes for bio-transformation. Toxins may be selective in the region of the adrenal affected, even within the different cortical zones, and thus identifying the affected regions may aid in determining the causative agent. Compounds such as aniline and sulfated muco-polysaccharides pre-dominantly target the zona glomerulosa, whereas the effects of toxins such carbon tetrachloride, acrylonitrile, clotrimazole and op'-DDD are largely confined to the zonas fasciculata and reticularis.[13] Toxicity affecting the adrenal medulla is relatively uncommon but has been reported with compounds such as reserpine, thiouracil and xylitol; cellular proliferative changes appear to be the most common manifestation of medullary toxicity.[13]

Non-toxic causes of adrenal degeneration may also occur. Hemorrhage and necrosis predominantly affecting the adrenal cortex has been observed in association with septic infections in humans, in particular those caused by *Neisseria meningitidis*, *Staphylococcus aureus* and streptococci. The pathogenesis of this condition - known as Waterhouse-Friederichsen Syndrome – is poorly understood, but it has been proposed that adrenaline release may induce both platelet aggregation and marked adrenal vasoconstriction, predisposing to venous thrombosis and infarction within the gland, particularly in association with concurrent disseminated intravascular coagulation.[9] Similar changes may be observed in septicemic horses[5] and calves[15], as well as in young lambs dying from exposure. Although possibly not completely analogous, adrenocortical hemorrhage may also be present in horses that die of during marked exertion. Adrenal hemorrhage has been induced experimentally in rabbits through intravascular endotoxin administration[8], but it is interesting to note that adrenocortical hemorrhage does not develop in

hypophysectomized animals treated with endotoxin, suggesting that the pathogenesis of Waterhouse-Friederichsen syndrome requires pituitary signaling. Thus, aberrant ACTH secretion may be a common factor in the pathogenesis of both trilostane toxicity and septic adrenal hemorrhage.

Table 1. Adrenal toxins (from Colby[4])

Acrylonitrile	Dilantin	Polyglutamic acids
ACTH	Dimethylbenzanthracenes	Ponceau SX
Aflatoxin	Estrogens	Pyrazole
Aminoglutethimide	Ethanol	Spironolactone
Aniline	Etomidate	Sulfated mucopolysaccharides
Bromocripitine	Fluphenazine	Suramin
Carbon tetrachloride	Hexadimethrine bromide	Tamoxifen
Chenodeoxycholic acid	Iprindole	Tetrachlorvinphos
Chloroform	Ketoconazole	Testosterone
Chlorphentermine	Mefloquine	Thioacetamide
Clotrimazole	Methanol	Thioguanine
Cyproterone	Nitrogen oxides	Toxaphene
Cysteamine hydrochloride	Parathion	Triparanol
op'-DDD	PBBs, PCBs	Urethane
Danazol	Polyanthosulfonate+ aminocaprionic acid	Zimelidine

JPC Diagnosis: Adrenal gland: Necrosis, cortical and medullary, diffuse, severe with hemorrhage, Saluki (*Canis familiaris*), canine.

Conference Comment: The word “adrenal” comes from the Latin for near (*ad-*) and kidney (*renes*) thus named for its relative location to the kidneys. An Italian anatomist, Bartolomeo Eustachi, is the individual credited with their discovery in 1563. However, his works were not received publicly until years later because they were secluded in the papal library. Eustachius (as he was known) along with Vesalius are considered the fathers of human anatomy. Due to religious restrictions on anatomists through the Renaissance, his anatomy book became a bestseller more than a century after his death.[3] His works are broken down into 17 “plates” in which he describes and illustrations the kidneys, ear, heart (including the vena azygous and vena cava, both named by him), thoracic and abdominal viscera, brain, spinal cord, and detailed descriptions of peripheral nerves.[14] In order to more clearly see the intimate structure and detail of these organs, Eustacius created magnifying glasses (early microscopes) and used different fluids to break down tissues. As you may expect, he also had extended knowledge of the inner ear, naming the Eustacian tube and diagraming the malleus, stapdius, and cochlea.[16]

The conference moderator discussed the submitted laboratory work, initially keying in on the azotemia (in which creatinine and urea are markedly increased), the elevated PCV (dehydration), and the urine specific gravity indicating dilute urine (1.018) with casts. Due to those findings, he favored renal rather than pre-renal azotemia. Conversely, he also

pointed out that there was no stress leukogram, which is abnormal for a sick dog and favors Addison's disease. After discussion with the contributor and reviewing the gross description of the kidney, the moderator concluded that this patient must have had concurrent renal disease which is what caused the clinical pathological findings. Additionally, he favors infarction of the gland rather than the toxic effects of trilostane administration. Conference attendees noted that trilostane is contraindicated in renal failure even though it is metabolized by the liver and excreted fecally.

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CASE IV: 4079-14 (JPC 4048433).

Signalment: Neonatal, male and female, Dorper (*Ovis aires*), ovine.

History: Of 36 pregnant ewes, 14 have lambed in the last week. The lambs (2) with goiters died within 10 minutes of birth. The normal lamb also died after birth. Examination of the ewe reveals a possible small thyroid swelling. All lambs were frozen before submission.

Gross Pathology: Examined at necropsy are two term affected lambs and an unaffected lamb. The lambs had been frozen and thawed prior to examination. The affected lambs externally have a large subcutaneous bulge in their anterior neck behind the larynx. The affected lambs are a female of body weight 2.2 kg and crown-rump length 31.1 cm and a male weighing 2.7 kg and having a crown rump length of 35.3 cm. The female affected lamb has a brachygnathic mandible. The unaffected lamb is a female of body weight 2.15kg and crown-rump length of 33.5 cm.

The unaffected lamb has a well-developed thick hair coat all over its body. The female affected lamb has no hair on the anterior aspects of the lower extremities, ventral abdomen or trunk. The only relatively normal hair is present on the neck, although there is also some hair on the posterior aspects of the legs below the elbow and stifle. The male affected lamb has similar alopecia on the anterior aspects of the front and rear legs, ventral body, and particularly scrotum, and a sparse, poorly developed hair coat on the trunk, especially on the posterior trunk. Hair on the head and neck is more normal.

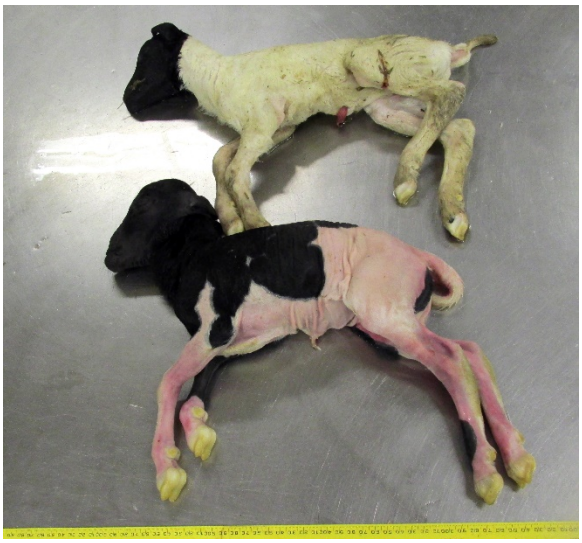
The female affected lamb has enlarged thyroids that are 7 cm long X 2.5 cm in greatest diameter and weigh 26.6 grams. The male's thyroids are 7 cm long X 3 cm in greatest diameter and weigh 2.15 grams. The enlarged thyroids are dark red in color and fleshy in texture. The left thyroid of the female contained a simple well defined cyst of 0.8 cm diameter located in the middle of the gland. The thyroids of the unaffected lamb are 2 X 0.7 cm and weigh 0.6 grams.

No visceral abnormalities are noted, including in the adrenals or pituitary. The eyes and brain are proportionally of normal size. The white matter of the spinal cord is a similar intensity of white between the affected and unaffected lambs.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): None provided.

Microscopic Description:

Thyroid gland: The thyroid follicles in both affected lambs are enlarged, sometimes spanning several 4X fields. The colloid has



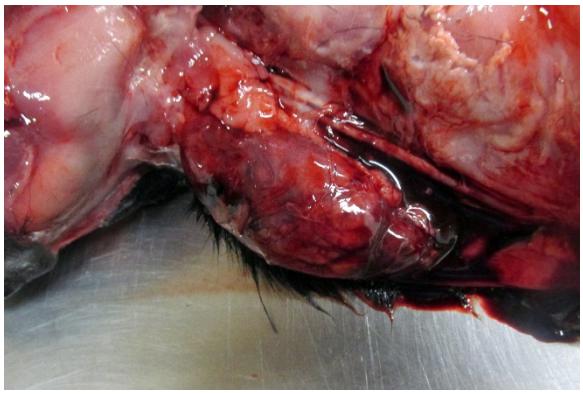
Thyroid gland, lamb. Two lambs (unaffected at top) are presented for examination. The affected lamb at bottom is alopecic over the anterior aspects of the lower extremities, ventral abdomen and trunk (Photo courtesy of: Veterinary Medical Diagnostic Lab, University of Missouri, www.VMDL.missouri.edu)

decreased eosinophilia and increased granularity. The follicular cells are frequently detached, although they remain at the periphery of follicles (freezing artifact). Interstitial cells are difficult to appreciate. The thyroid from the unaffected lamb has isomorphic follicles containing moderately eosinophilic colloid and a layer of cuboidal cells lining each. There is mild to moderate sloughing of colloidal epithelium (freezing artifact).

Skin: Affected lambs have reduced numbers of hairs protruding from the follicles. In some affected sections the epidermis is thinner and the hairs are farther apart, with mild myxedema of the deep dermis. In some sections there is basophilic ground substance consistent with myxedema in the upper dermis as well.

Contributor's Morphologic Diagnosis:
Colloid goiter
Epidermal atrophy with alopecia
Contributor's Comment: This case demonstrates congenital goiter and the alopecic skin disease that often is present.

Goiter or thyroid hyperplasia can result from multiple mechanisms: iodine deficiency, ingestion of goitrogenic compounds that interfere with thyroxine production, excess iodide and genetic mechanisms that interfere with biosynthesis of thyroid hormones.[2] All of these etiologies result in activation of the hypothalamus as a result of low T3 and T4, with the result of increasing TSH. Common goitrogenic plants include thiouracil, sulfonamide and plants of the Brassica group. Offspring of deficient dams develop severe bilateral thyroid enlargement as in this case, with hyperplasia and hypertrophy of thyroid follicular cells and enlargement of interstitial blood vessels. Increased iodide blocks release of T3 and T4, resulting in enhanced TSH secretion.[2]



Thyroid gland, lamb. Thyroids in the affected glands are dark red, fleshy, and measure 7cm in length. (Photo courtesy of: Veterinary Medical Diagnostic Lab, University of Missouri, www.VMDL.missouri.edu)

Hypothyroidism in animals, including sheep, and people can result in abortions, stillbirths and congenital abnormalities.[2]

In hyperplastic goiter, follicles vary in size; colloid is hypereosinophilic and may be vacuolated. Follicles are lined by one or more layers of epithelium, with small basal nuclei. Finger-like projections of cytoplasm may protrude into the follicle lumens. In these lambs, the colloid was pale and several large cysts were present. Following correction of the problem, the gland may become pale, as reduced TSH reduce endocytic resorption of colloid and condition is called colloid goiter.[4]

Thyroxine or T4 is the major product of the thyroid gland but is not active as an effective transcription factor. T4 must be deiodinated to T3 before it can bind to the nuclear receptor and the reaction regulated the bioavailability. Sulfation may also play a role in fetal thryoxine metabolism, as the addition of sulfate accelerates deiodination to inactive metabolites. Sulfation is upregulated during gestation in sheep during the last trimester and may regulate the supply of fetal T3 and facilitate maternal-fetal exchange. Iodine is concentrated by the placenta during fetal life.[7] Glucuronidation of thyroxine occurs in

liver and precedes biliary-fecal excretion. Stimulation of glucuronidation by various drugs can produce goiter in rats, but not humans.[7]

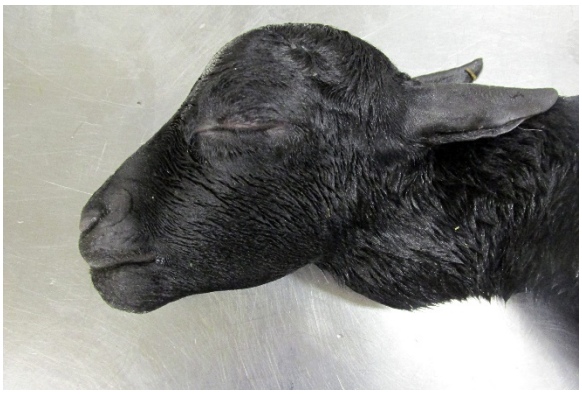
Congenital dyshormonogenetic goiter is inherited as an autosomal recessive trait in Corriedale, Dorset Horn, Merino and Romney sheep,[3,5] Afrikaner cattle, and dwarf Saanen goats. Dorset horn sheep form part of the Dorper lineage. Inheritance is believed to be autosomal recessive in sheep. The most obvious changes in these sheep, besides thyroid enlargement, were abnormalities of the skin. Affected fetuses have abnormal hair coat, myxedema of the subcutis, weakness, and most die after birth. Thyroid follicles are described as collapsed due to lack of colloid,[2] because there is increased endocytic activity and diminished ability to synthesize thyroglobulin. Iodine uptake is increased but blood T3 and T4 are low. The antibody used to stain for thyroglobulin was not optimized for sheep, but there was at least some staining of affected lambs' thyroids. Unfortunately freezing and thawing of the tissue caused considerable artifact, which may have interfered with staining.

Under long term TSH stimulation, albumin and other proteins are iodinated by the thyroid. Iodine supplements restore normal thyroid hormone levels in affected sheep, even though thyroglobulin is absent. However, affected offspring die shortly after birth. Thyroglobulin RNA transcripts are incorrectly processed and no full-length protein results, yet the product is immuno-reactive with anti-thyroglobulin polyclonal antibodies[3] and IHC may not be a definitive differentiating test.

Few studies have been done on the histogenesis of fetal skin lesions during maternal hypothyroidism. Primary changes in rat skin include a significant decrease in epidermal thickness and reduction of hair follicle numbers.[1] In addition, there is increased laminin deposition in the dermis and particularly the basement membrane.[1] Laminin is important in connecting the dermis and epidermis. Hypothyroid rat pups developed increased laminin by 10 days of age. Number of hair follicles decreased and myxedema is present as in the skin of these lambs. Laminin is important to hair follicle development; T3 increases hair follicle survival in vivo considerably.

JPC Diagnosis: 1. Thyroid gland, follicular epithelium: Hyperplasia, diffuse, severe, Dorper (*Ovis aires*), ovine.
2. Haired skin, superficial dermis: Myxedema, diffuse, moderate.

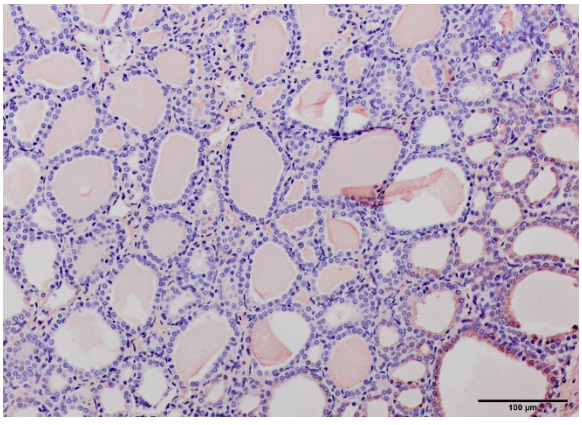
Conference Comment: Synthesis of thyroid hormone is unique among the other endocrine organs because hormone assembly occurs extracellularly within the lumen of the thyroid follicle. Iodide ions (I^-) are collected from plasma by follicular cells, transported to the follicular lumen, and oxidized to iodine (I_2). Thyroglobulin, a high-molecular-weight glycoprotein, is synthesized by follicular cells and contains tyrosine, which is an essential component of thyroid hormones and



Thyroid gland, lamb. The affected lamb has a subcutaneous bulge in the ventral neck. . (Photo courtesy of: Veterinary Medical Diagnostic Lab, University of Missouri, www.VMDL.missouri.edu)

aids in their assembly as follows: Iodine binds tyrosyl residues in thyroglobulin to form monoiodotyrosin (MIT) followed by diiodotyrosine (DIT) which are coupled together to form T4 and T3 which is secreted by the thyroid gland in response to the hypothalamic-pituitary-thyroid axis (HPTA). The hypothalamus initiates the process by secreting thyrotropin-releasing hormone (TRH) which acts on the pituitary which releases thyroid stimulating hormone (TSH). TSH stimulates secretion of T3 and T4 from thyroid follicles. T3 and T4 act as a negative feedback mechanism to inhibit TSH release from the pituitary and induce somatostatin release from the hypothalamus which also inhibits TSH release from the pituitary. Additionally, T4 is converted to T3 within the pituitary gland and hypothalamus.[6]

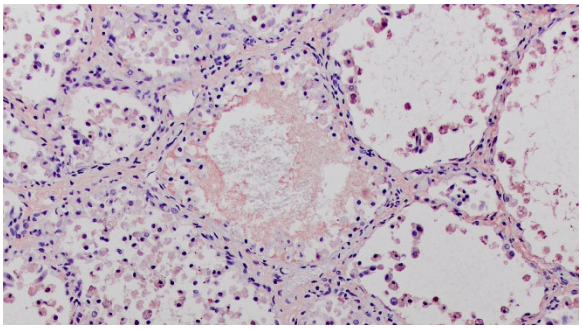
Non-neoplastic and noninflammatory hyperplasia of the thyroid gland is termed "goiter" and is due to several pathogenic mechanisms: iodine deficiency or excess, goitrogenic compounds that interfere with thyroid hormone synthesis, and genetic enzyme defects in thyroid hormone synthesis. It is interesting that both deficiency of and excess iodine result in goiter. This is because iodine is required for synthesis of thyroid hormones, but, conversely, excess iodine interferes with fusion of colloid droplets and lysosomal bodies, blocking the release of thyroid hormones.[6] The rest of these pathogenic mechanisms are described in detail by the contributor.



Thyroid gland, lamb. Follicles are larger than in the unaffected lamb, isomorphic and colloid-filled, but (Photo courtesy of: Veterinary Medical Diagnostic Lab, University of Missouri, www.VMDL.missouri.edu)

Newborns with goiter have unique gross characteristics such as: myxedema, alopecia, swollen tongue and laryngeal edema. The latter often contribute to death in newborns with goiter due to asphyxia and suffocation. The effect on the dam is often minimal except for prolonged gestation, dystocia, and retained placenta on occasion.[6]

True diffuse goiter must be distinguished from nodular hyperplasia, which is a fairly common finding in older horses, cats and dogs, appearing grossly as variably sized white nodules. In most animals, these nodules are not hormonally active, except in cats where they are typically functional.[6]



Thyroid gland, lamb. Previous freezing has resulted in detachment of colloid epithelium and colloid granularity in some areas of the slide. (Photo courtesy of: Veterinary Medical Diagnostic Lab, University of Missouri, www.VMDL.missouri.edu)

The diffuse myxedema within the superficial dermis is prominent in the submitted sections of skin from the affected animal. Evaluation of hair follicles in the absence of age-matched control or the unaffected lamb proved more problematic for attendees. While there are some focal areas in which hair follicles appear decreased in number,

follicles do not show obvious signs of hypoplasia.

Contributing Institution:
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www.VMDL.missouri.edu

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