Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #9 2 November 2022

CASE I:

Signalment:
11½ -year-old, spayed female, American Bulldog, canine (*Canis lupus familiaris*)

History:
Two years ago, this canine presented for routine examination and recent increased urination. Ultrasound confirmed mass-like lesions at the trigone and the neck of the urinary bladder. The attending veterinarian suspected transitional cell carcinoma at the time. The owners elected for conservative treatment, so the canine was started on nonsteroidal anti-inflammatory drugs (NSAIDs), famotidine, omeprazole, and gabapentin.

Four months ago, the canine started coughing intermittently. Radiographs revealed multiple chest masses with metastatic pattern and osteophytes of the left distal humerus, suspicious of an early metastatic lesion.

A month later, the canine presented with lameness on the right front paw. Radiographs revealed periosteal reaction and sclerosis in the 2nd metacarpal bone. Not long after, euthanasia was elected due to pain on the right front limb and poor quality of life.

Gross Pathology:
This is the carcass of a 31 kg spayed over-conditioned female canine with no autolysis.

The lungs have a dozen variable-sized firm masses, ranging from 1 cm scattered throughout to a large 12x10 cm obliterating 50% of the caudal left lobe. The masses are bulging, well demarcated and off-white pale to reddish in color. They are distending and replacing the normal pulmonary parenchyma. The mediastinal lymph nodes are enlarged (1 cm x 5 cm) and flat in shape. On cut section, there are small white nodules (0.3 cm).

The kidneys are within normal limits. The urinary bladder mucosa at the level of the trigone has a soft, 1 cm thick, off-white, fuzzy irregular layer that covers 5 cm around the trigone extending into the urethra. The fundus of the bladder has three masses up to 1.5 cm in diameter that are firm, nodular and protruding.

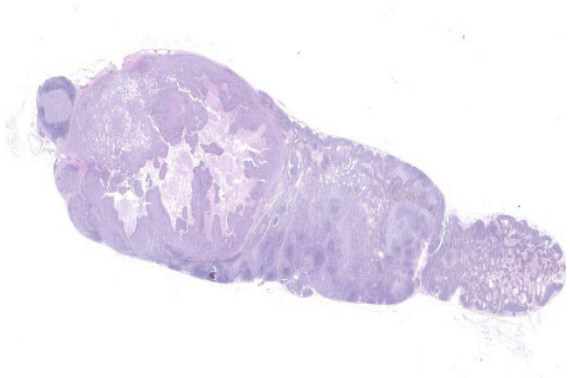

Figure 1-1. Lymph node, dog. A section of lymph node is submitted for examination. There is a large neoplasm which effaces 50% of the node (left). (HE, 6X)

Other lymph nodes, right axillary, mesenteric and retroperitoneal, are firm and slightly enlarged.

The liver has a diffuse, mild reticular pattern with occasional white pale well-demarcated foci (up to 0.5 cm).

The free edges of the left atrioventricular valve have multiple variable-sized nodules (1 mm) with a smooth surface.

The second right metacarpal bone has a 3 cm in diameter hard mass that extends into the proximal phalanx and the distal carpal bone. Upon opening the bone, the mass is necrotic and extends and effaces the carpal bone.

Laboratory Results:
No findings reported.

Microscopic Description:
Lymph node- mediastinal: There is a well-demarcated unencapsulated expansile nodule that effaces the normal follicular lymphoid architecture. The nodule is composed of fronds of thick undulating ribbons of tightly packed neoplastic cells supported by a fine fibrovascular stroma.

Neoplastic epithelial cuboidal to polyhedral cells with abundant pale eosinophilic cytoplasm. The cells show moderate anisokaryosis and anisocytosis with occasional megalokaryosis. There are areas where the cells are less compacted and the cytoplasm has variable-sized empty vacuoles. Occasionally, the large vacuoles displace the nucleus to the periphery. Some of the vacuoles occasionally contain a homogenous granular material. The core of the neoplastic nodule has a large necrotic area.

There are 20 mitotic figures in 10HPF (40x), with a moderate number of aberrant mitotic figures.

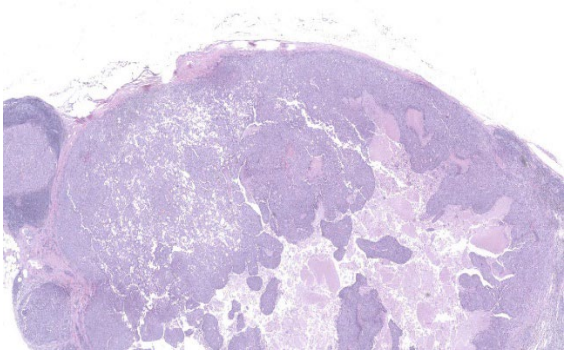

Figure 1-2. Lymph node, dog. There are large areas of necrosis within the metastatic neoplasm. (HE 18X)

There are small nodules of neoplastic cells in the subcapsular sinuses. These nodules are present only in some of the sections.

Contributor's Morphologic Diagnoses:
Lymph node: metastatic transitional cell carcinoma/urothelial carcinoma

Contributor's Comment:
Transitional cell carcinoma (TCC), or urothelial carcinoma (UC), is a malignant tumor that originates in the transitional epithelium of the urinary tract. Squamous and glandular carcinomas can also occur. The urinary bladder is the most common site of the lesion, but it can occur anywhere form the renal pelvis to the distal urethra. Within the urinary bladder, TCC is most commonly diagnosed in the trigone area. TCC mostly occurs in cats and dogs. Bladder neoplasms are rare in horses, sheep, goats, and pigs.

Carcinomas in the urinary bladder can be classified in broad groups: Urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma. This is based on the predominant cell type or the organization of the lesion. Urothelial carcinomas (UC) can be further classified based on their patterns of growth as papillary (project into the lumen), flat, degree of anaplasia (graded on a scale of 1-4), and degree of infiltration (infiltrating or noninfiltrating).

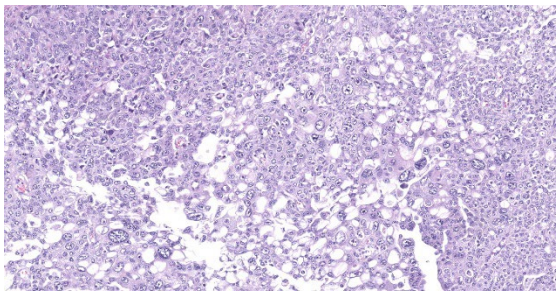

Figure 1-3. Lymph node, dog. In some areas of the tumor, closely-packed tubules lend a "sieve-like" appearance. (HE, 162X)

Most TCCs are intermediate to high-grade papillary infiltrative tumors.

TCC/UC tend to occur in older dogs (average 9-11 years). There is an approximate 2:1 ratio of female: male for bladder neoplasm but this is not always a consistent finding. However, neutered dogs seem to be predisposed to bladder neoplasms. Some breeds, like Scottish terriers. Airedales, Shetland sheepdogs, West Highland white terriers, fox terriers or beagles, have a high risk for TCC/UC than other dogs.

Of all the canine cases of TCC/UC, 90% demonstrate clinical signs. These signs include hematuria, pollakiuria, cystitis or dysuria. These urinary system clinical signs are not unique to neoplasms. Other clinical signs that are not related to the urinary system are mostly due to metastasis. These can include lameness due to bone metastasis or hypertrophic osteopathy, or dyspnea due to pulmonary metastasis.

Most of the literature suggests that tumors of the urinary bladder are less common in cats than in dogs. Cats with TCC/UC are usually older (6-18 years). Most of the clinical signs relate to the lower urinary tract: hematuria, stranguria, dysuria, and pollakiuria. Current urinary tract infection is present in over 70% of the cats with TCC.

If TCC/UC is suspected, the diagnostic work-up should include complete blood count, serum biochemistry profile, urinalysis, urine culture, radiographs (thorax and abdomen), and bladder imaging. Urine should be collected only by free catch or bladder catheterization. Ultrasound is useful to assess the bladder wall thickness but also for viewing regional lymph nodes and other abdominal organs for metastases. A diagnosis of TCC/UC requires histopathologic confirmation.

It can be difficult to differentiate tumors in the prostatic region of male dogs as urothelial origin or prostatic origin. About 30% of TCC/UCs are in the prostate and in neutered dogs it is the most common prostatic tumor. This should be carefully considered when determining the origin of a neoplasia in the prostatic region. Factors that favor TCC/UC Melamed-Wolinska bodies, UPIII immunoreactivity, CK7 immunoreactivity, desmoplasia, and widespread metastasis.

High grade, invasive TCC/UCs are among the most malignant neoplasms and cause death via metastasis and cachexia. Upon diagnosis in canine patients, about 20% have detectable pulmonary metastases, 15% have lymph node metastases, and 6% have lumbar or pelvic bone metastases. In addition, squamous or glandular metaplasia may be important in the prediction of metastases.

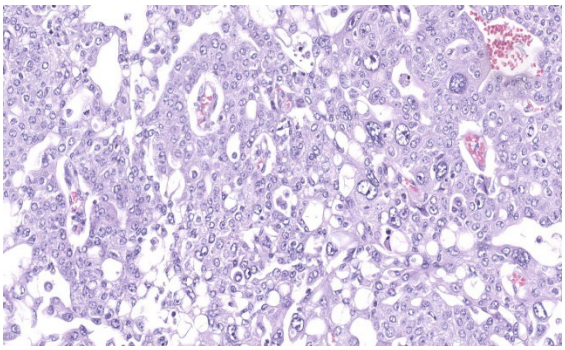

Figure 1-4. Lymph node, dog. There is multifocal nuclear pleomorphism and gigantism scattered throughout the tumor. (HE, 284X)

Prognosis of dogs with TCC/UC is grave. Less than 20% of treated dogs live more than one year.

In humans, most of the cancer associated death, approximately 90%, are caused by metastatic disease rather than primary tumor. The effort to further characterize the neoplastic dissemination has expanded the research in carcinogenesis. First, to understand the metastatic dissemination behind this process, a sequence of a multi-step process of invasion is proposed: the metastatic cascade: 1) epithelial primary neoplastic cell invasion into the surrounding stroma tissue and extra cellular matrix; 2) epithelial cell intravascular invasion; 3) neoplastic epithelial cells need to survive during circulatory transit. 4) neoplastic cell arrest and extravasation through vascular walls and into the parenchyma or distant tissue; 5) formation of microneoplastic colonies. Second, in addition to the metastatic cascade, the neoplastic cells need to be transformed and the concept of epithelial mesenchymal transition (EMT) has been expanded to further characterize carcinogenesis. EMT is a complex biological process where the epithelial cells acquire new properties to successfully invade tissue. These properties include 1) increased motility invasion and 2) ability to degrade extracellular matrix. These EMT properties show at different levels depending on the tissue site and the degree of malignancy. EMT is orchestrated by different tissue transcription factors starting with EMT-inducing transcription factors (EMT-TFs) such as SNAIL, SLUG, or ZEB1. There is still controversial evidence about how much these biological process are involved in metastasis. The other current metastatic process is the dormant niche, where dormant disseminated tumor cells will reside within the site of stem cells and somehow will be protected.

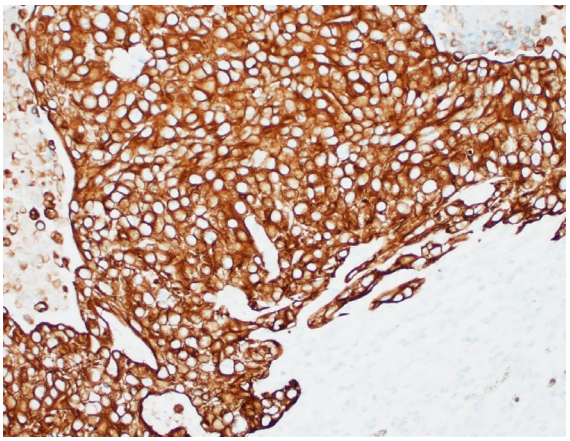

Figure 1-5. Lymph node, dog. Neoplastic cells demonstrate strong cytoplasmic immunopositivity for cytokeratin. (anti-AE1/AE3, 284X)

Primary and metastatic tumors of the bladder occur in dogs and rarely in cats; several tumor types have been reported. Hematuria is a common sign. Metastatic bladder neoplasia is rare but some of the signs listed below are

due to metastases. It has been associated with hypertrophic osteoarthropathy. Systemic signs of urinary obstruction are seen if urine flow at the trigone is blocked. Tumor cells might be present in the urine. Benign polyps of the urinary bladder induce clinical, laboratory and radiographic characteristics similar to neoplasia of the bladder.

Transitional cell carcinoma (TCC) is the most common cancer of the bladder in dogs. Tumors most commonly originate in the trigone, but they can also occur or extend through the urethra. The most common metastatic sites are the iliac and other abdominal lymph nodes, liver and lung. Ultrasonography of the abdomen is done to measure the size of the tumor and look for metastases within the abdomen. When the tumor is accessible, surgery is the best option to prolong survival for dogs with TCC when followed by chemotherapy. Regardless of whether surgery is possible or not, chemotherapy has been shown to alleviate symptoms and prolong survival for many dogs with TCC.

Contributing Institution:
https://www.westernu.edu/veterinary/

JPC Diagnosis:
Lymph node: Urothelial carcinoma, metastatic.

JPC Comment:
Recently, a urine assay measuring the $BRAF^{V595E}$ mutation was developed that provides clinicians with a non-invasive means of differentiating cystitis from neoplasia.[3,8] The BRAF assay has a high sensitivity and sensitivity for the mutation, which affects approximately 70% of dogs with urothelial carcinoma.[3,8] The $BRAF^{V595E}$ mutation in dogs is analogous to the $BRAF^{V600E}$ mutation in many human cancers. The mutation causes constituent activation of the MAPK pathway, preventing apoptosis of neoplastic cells and increasing invasiveness and metastasis.[8] A few recent studies found no significant difference in survival times in UCs with and without the $BRAF^{V595E}$ mutation; the mutation does, however, make the neoplasm more amenable to treatment. Dogs with $BRAF^{V595E}$ mutation treated with chemotherapy or both chemotherapy and surgery had double or triple the survival times, respectively, compared to dogs treated with NSAID therapy alone.[5]

In dogs, the BRAF mutation has also been associated with increased CCL17 expression, which is significantly higher than levels in healthy dogs or dogs with non-neoplastic urinary disease.[8] This is due to overexpression of COX-2 by neoplastic cells, which stimulates production of PGE-2 and upregulation of CCL17. [8] The end effect of CCL17 elevation is infiltration of Foxp3+ regulatory T cells (T-reg) within and surrounding the neoplasm.[8] In many cancers, T-regs are associated with a poor prognosis, possibly due to inhibition of antitumor immune activity.[8]

The overproduction of COX-2 by neoplastic cells has made NSAIDs, such as peroxicam, one of the main therapeutic agents used to prolong UC survival times.[4,8] A recent study found LOX-5 was similarly overproduced by comparing immunohistochemistry scores of UC, cystitis, and normal bladder mucosa.[4] These results suggest that NSAIDs with anti-LOX-5 activity may provide another target for prolonging survival times and should be investigated further.[4]

References:

1. Anesi S, Parry AT, Monti P, Elliott J. Radiographic appearance of an osseous metastasis to the distal radius from a transitional cell carcinoma of the urinary bladder. *Veterinary Record Case Reports*. 2017; *5*(4): p.e000474.
2. Epstein JI, Lotan TL. The Lower Urinary Tract and Male Genital System. In: Kumar V, Abbas AK, Aster JC, eds: *Robbins and Cotran Pathologic Basis of Disease.* Philadelphia, PA: Elsevier Saunders. 2015: 976-981.
3. Ettinger S. Urine luck: A new test for canine bladder and prostate cancer. *DVM360.* July 29, 2019. Accessed October 16, 2020. https://www.dvm360.com/view/urine-luck-new-test-canine-bladder-and-prostate-cancer
4. Finotello R, Schiavo L, Ressel L, Frohmader A, Sivlestrini P, Verin R. Lipoxygenase-5 Expression in Canine Urinary Bladder: Normal Urothelium, Cystitis and Transitional Cell Carcinoma. *J Comp Path*. 2019; 170:1-9.
5. Gedon J, Kehl A, Aupperle-Lellbach H, von Bomhard W, Schmidt JM. BRAF mutation status and its prognostic significance in 79 canine urothelial carcinomas: A retrospective study (2006-2019). *Vet Comp Oncol.* 2022; 20(2):449-457.
6. Knapp DW, McMillan SK. Tumors of the Urinary System. In: Withrow SK, Vail

DM, Page RL, eds: Withrow & MacEwen's Small Animal Clinical Oncology. St. Louis, MO: Elsevier Saunders. 2013; 572-582.
7. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. *Cell*. 2017; 168(4): 670-691.
8. Maeda S, Yoshitake R, Chambers JK. $BRAF^{V595E}$ Mutation Associates CCL17 Expression and Regulatory T Cell Recruitment in Urothelial Carcinoma of Dogs. *Vet Pathol.* 2021; 58(5): 971-980.
9. Marvel SJ, Séguin B, Dailey DD, Thamm DH. Clinical outcome of partial cystectomy for transitional cell carcinoma of the canine bladder. *Veterinary and Comparative Oncology*. 2017; 15(4): 1417-1427.
10. Meuten DJ, Meuten TLK. Tumors of the Urinary System. In: Meuten DJ, ed: *Tumors in Domestic Animals*. 5th edition. Ames, IO: John Wiley & Sons, Inc. 2017; 666-675
11. Mittal V. Epithelial mesenchymal transition in tumor metastasis. *Annual Review of Pathology: Mechanisms of Disease*. 2018; 13: 395-412.
12. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. *Cell*. 2011; 147(2): 275-292.

CASE II:

Signalment:
10 year-old, male, castrated, German wirehaired pointer (*Canis lupus familiaris*)

History:
During the CT scan of the cervical vertebra, a mass in the thyroid was seen

Gross Pathology:
Excision of a beige-brown egg-shaped tissue fragment measuring 3.3 x 2.1 x 1.9 cm. This one appears to be encapsulated. In cross section, the fragment has a beige-brown aspect.

Laboratory Results:
No findings reported.

Microscopic Description:
Thyroid gland: There is a predominantly solid, locally infiltrative and encapsulated, moderately cellular epithelial neoplasm. Focally, the neoplastic infiltrate appears to extend into the surgical excision margin. The majority of the neoplastic cells grow in contiguous fields, nests and trabeculae and have a rounded to polygonal shape with a very substantial amount of eosinophilic and finely granular cytoplasm with a moderately sized, slightly varying rounded nucleus. In addition to the neoplastic cell component, varying sizes of fields and trabeculae, neoplastic cells with no apparent eosinophilia of the cytoplasm with predominantly larger, hypochromatic nuclei are also observed. In some places, both cell populations are found in close proximity to each other. In several areas, the neoplastic infiltrate shows growth through the surrounding connective tissue capsule with bulging fields of neoplastic cells in vascular lumens. In addition, in several places in the periphery, incisions of pre-existent, inactive thyroid tissue are seen. Mitoses

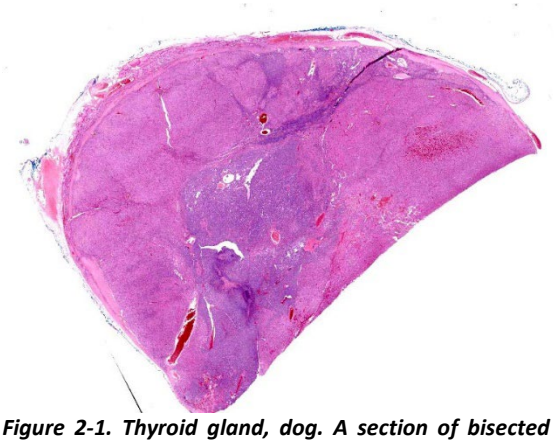

Figure 2-1. Thyroid gland, dog. A section of bisected thyroid gland is submitted for examination. The gland is markedly enlarged and the architecture is effaced by a multilobular neoplasm. (HE, 5X)

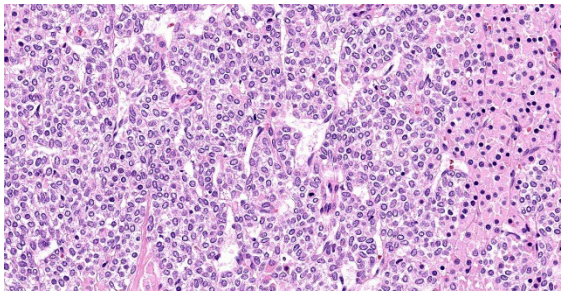

Figure 2-2. Thyroid gland, dog. The neoplasm is composed of polygonal cells which are arranged in nests and cords. At right, neoplastic cells transition into a separate morphology with abundant finely granular eosinophilic cytoplasm (Hurthle cells). (HE, 363X)

are rare and there is mild anysokaryosis and anysocytosis.

Contributor's Morphologic Diagnoses:
Thyroid, Hurtle-cell carcinoma

Contributor's Comment:
Between 10 and 15% of the neoplasms located in the head and neck in dogs are originating from the thyroid.[3] Those neoplasms can be unilateral (most frequent) or bilateral and are often palpable near the larynx as a firm or soft mass.[8,10] Most thyroid carcinomas are nonfunctional.[8] Thyroid carcinoma is the most common and most frequently diagnosed[15] endocrine malignancy in dogs[8] representing 19% of thyroid tumors with up to 38% of metastasis, most of them are already present by the time of diagnosis.[15] Some breeds are thought to be predisposed as Boxers, Beagles, Siberian Huskies and Golden retrievers[10,15] although in one study mixed breeds tend to be more affected.[15] The age ranges from 9 up to 15 years[8,15] without sex prevalence.[10]

Differences between carcinomas and adenomas are essentially based on the size of the neoplasm, adenoma being usually smaller. Thyroid carcinomas are fixed due to local invasion, whereas thyroid adenomas are subcutaneously freely movable.[10] Carcinomas are usually multinodular and often show central necrosis and hemorrhages.[15] Early carcinomas tend to be well demarcated and later carcinomas lead to vascular invasion in 45% of the cases[8], essentially into the branches of the cranial and caudal thyroid veins forming large tumor cell thrombi[10] and resulting in an impossible surgical resection.[8] Dogs and humans show similarities in the spontaneous development of thyroid carcinoma with metastases to the lungs although the incidence of metastases in dogs is higher by the time of the diagnosis.[8] Risks of metastasis are likely to increase with the size of the neoplasm.[8] Pulmonary metastases will often precede retropharyngeal and caudal cervical lymph nodes involvement.[8]

Thyroid tumors, in dogs, are classified according to the World Health Organization (WHO) based on the morphological features.[7,15] Thyroid tumors can arise from either thyroid follicular cells or thyroid C-cells (parafollicular cells, chief cells). The latter cell type is considered to represent less than 5% of thyroid neoplasms in dogs.[8]

Thyroid follicular cell carcinomas are subdivided in different subtypes:
-- cells are forming follicular structures consisting of cubic or columnar epithelial with or without colloid[3,7], the so-called compact cellular (solid) showing cells with centrally localized nuclei and pale eosinophilic and granular cytoplasm.

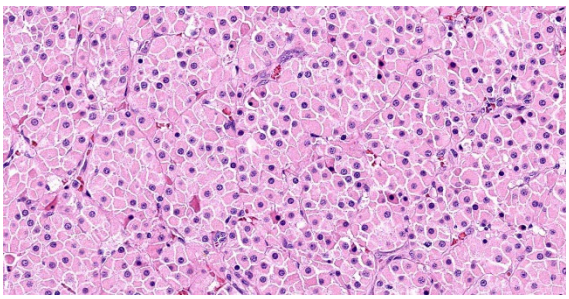

Figure 2-3. Thyroid gland, dog. Some lobules of the neoplasm are completely composed of Hurthle cells. (HE, 381X)

-- the presence of both follicular and solid areas refers to follicular-compact cellular carcinoma.[3,7]
-- papillary structures made of multiple lines of cubic cells extending into cystic spaces surrounded by fibrovascular stroma are so called papillary carcinoma.[3,7]

Follicular thyroid carcinoma can be also classified as well-differentiated, poorly differentiated, undifferentiated or carcinosarcoma.[3]

In the dog, tumors with granular cytoplasm staining brightly eosinophilic with hematoxylin and eosin (HE) include granular cell tumors, rhabdoid tumors, neuroendocrine tumors, and oncocytomas. Oncocytomas are rare, usually benign, tumors composed of oncocytes. Oncocytes[2] also called Hurthle cells or oxyphilic cells, are large, polygonal cells originating from metaplastic transformation of mature glandular or non-glandular cells. The high number of mitochondria present give the appearance of the abundant eosinophilic cytoplasm. Additionally, the cells composing the neoplasm can show a granular eosinophilic cytoplasm will refer to the Hurthle cell tumor and are rarely seen in dogs.[7] In the dog, oncocytomas have been reported originally in the larynx but also in the thyroid gland and in the kidney. Specific immunohistochemical markers are helpful in making a differential diagnosis. Oncocytomas specifically express cytokeratin. Additionally granular cell tumors are positive for vimentin and are negative for epithelial cell markers.[2]

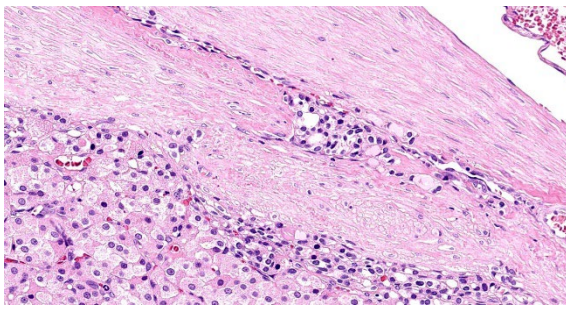

Figure 2-4. Thyroid gland, dog. Neoplastic cells invade the surrounding capsule. (HE, 361X)

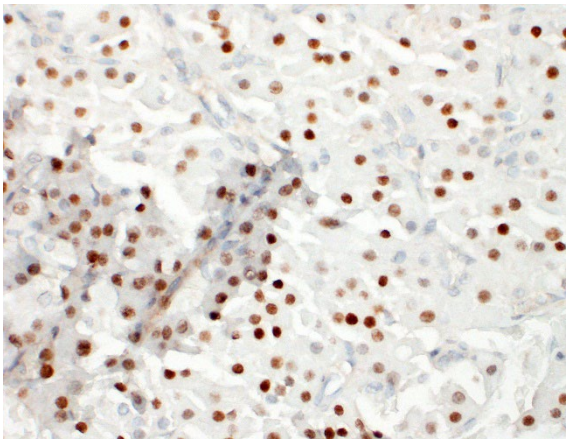

Figure 2-5. Thyroid gland, dog. Neoplastic cells demonstrate moderate nuclear positivity for thyroid transcription factor -1. (anti-TTF-1, 400X)

This is a phenomenon of metaplasia that occurs in inflammatory disorders, such as thyroiditis, or other situations that result in cellular stress. The proliferation of oncocytes gives rise to hyperplastic and neoplastic nodules. Oncocytic cells in the thyroid are often called “Hürthle” cells; however, this is a misrepresentation because they were initially described by Askenazy, and the cells that Hürthle described were in fact C cells.[1]

Numerous studies indicated that the criteria that apply to follicular tumours of the thyroid also distinguish malignant from benign Hürthle cell lesions. These included capsular and vascular invasion.[1]

To differentiate follicular cell carcinoma from C-cell carcinoma immunohistochemistry (IHC) might be necessary. In general, C-cell thyroid carcinomas exhibit strong immunoreactivity to calcitonin, calcitonin gene-related peptide (CGRP), and napsin A or markers of neuroendocrine tissue (Hassan, Campos). While follicular cell thyroid carcinomas show positivity for thyroglobulin, Pax8, and thyroid transcription factor (TTF-1 or NKX2). With the Papanicolau stain, the cytoplasm may be orange, green, or blue. By electron microscopy, the cytoplasmic granu-

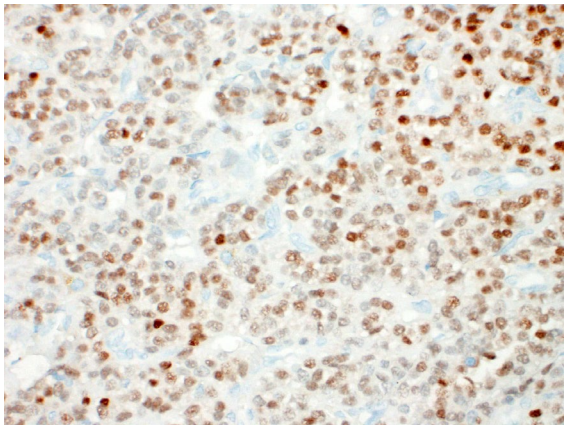

Figure 2-6. Thyroid gland, dog. Neoplastic cells demonstrate moderate nuclear positivity for PAX-8. (anti-PAX-8, 400X)

larity is produced by large mitochondria filling the cell, consistent with oncocytic transformation.[1]

The metastatic rate of thyroid carcinoma in dogs is highly related to the volume of the tumor (>20 cm^3), bilateral and cervical vascular invasion[3]. More recently other factors the presence of estradiol in cells expressing estrogen receptors[15] and to a greater protein expression of factors related to proliferation and angiogenesis (TTF-1, PCNA and VEGF).[13]

Thyroid cancers in dogs can either be inherited or spontaneous. In some breeds as the Dutch German longhaired pointers, two deleterious recessive mutations in the TPO gene have been highly associated with the familial follicular cell carcinoma[16]. Other studies suggest that overexpression of VEGFR-1, VEGFR2, PDPK-1, AKT1, and AKT2 in canine follicular thyroid carcinoma and VEGFR-1, EGFR, and PIK3CA in canine medullary thyroid carcinoma suggests that the PI3K/Akt signaling pathway is activated and increased in the pathogenesis of thyroid cancer in dogs for both follicular thyroid carcinoma and medullary thyroid carcinoma. Missense mutations in K-RAS were occasionally identified in a follicular thyroid carcinoma and a medullary thyroid carcinoma which are likely to be relevant for thyroid gland tumorigenesis.[4]

In cats, thyroid carcinomas tend to be rare and occur much less frequently than adenomas or multinodular hyperplasia[10]. Metastases to regional lymph nodes and distant sites, unlike in dogs, are rarely reported in cats.[8]

Contributing Institution:
Informatie voor dierenartsen - Veterinair Pathologisch Diagnostisch Centrum - Universiteit Utrecht (uu.nl)

JPC Diagnosis:
Thyroid gland: Hurthle cell tumor.

JPC Comment:
The contributor provides a thorough review of thyroid neoplasia and a slightly more nebulous entity – the oncocytoma. The unique dual morphology of neoplastic cells drove spirited discussion amongst conference participants, with some initially considering the possibility of a collision tumor or parathyroid origin. A collision tumor was ruled out by the areas of gradual transition between the two morphologies and the lack of a capsule separating them.

This week's moderator, Dr. Donald Meuten, explained the criteria for lymphovascular invasion in the Veterinary Cancer Guidelines and Protocols reference guide: (1) intravascular tumor with a thrombus adhered, (2) neoplastic cells invading the wall and endothelium, (3) neoplastic cells surrounded by endothelium, and (4) neoplastic cells in a vessel confirmed by vascular immunohistochemistrical stains, with the first two criteria supported by more firm evidence in the literature. Traditionally, infiltration and capsular invasion have also been considered criteria of malignancy in thyroid follicular neoplasms. In this case, the moderator and conference

participants did not favor a diagnosis of malignancy and opted to diagnose a tumor instead of a carcinoma.

As the contributor mentions, in the dog, oncocytomas have been reported in the larynx, thyroid, and kidney, and are most commonly found in the salivary gland.[12] In cats, oncocytomas have been found in the salivary glands and periocular tissues.[5] Additionally, there are rare reports in the nasopharynx and choroid plexus.[5,6,17]

Histologically, the main differential diagnoses for oncocytomas are granular cell tumors and rhabdomyomas. Granular cell tumors have been documented in the oral cavity, lung, pharynx, and brain, and are generally benign.[11] Cytoplasmic granules in both oncocytomas and granular cell tumors are PAS positive; however, electron microscopy reveals them to be different structures; mitochondria in the former, and probably secondary lysosomes in the latter.[11] Differentiation of rhabdomyomas may require immunohistochemical staining to confirm muscle origin.[11] Another differential diagnosis in the kidney is a chromophobe renal cell carcinoma.[11] This rare neoplasm is believed to originate from the intercalated cells of the collecting ducts; is negative for pancytokeratin and PAS; and is positive for vimentin, colloidal iron, and CD117.[12]

References:

1. Asa SL. My Approach to Oncocytic Tumours of the Thyroid. *J Clin Pathol.* 2004; 57(3): 225-232.57, no. 3 (1 March 2004): 225–32.
2. Buergelt CD, Adjiri-Awere A. Bilateral Renal Oncocytoma in a Greyhound Dog. *Vet Pathol.* 2020; 37(2):188-192.
3. Campos M, Ducatelle R, Rutteman G, Kooistra HS, Duchateau L, de Rooster H, Peremans K, Daminet S. Clinical, Pathologic, and Immunohistochemical Prognostic Factors in Dogs with Thyroid Carcinoma. *Jour Vet Intern Med.* 2014;28(6):1805-1813.
4. Campos M, Kool MMJ, Daminet S, Ducatelle R, Rutteman G, Kooistra HS, Galac S, Mol JA. Upregulation of the PI3K/Akt Pathway in the Tumorigenesis of Canine Thyroid Carcinoma. *Jour Vet Intern Med.* 2014; 28(6):1814-1823.
5. Cossic B, Silver G, Kent M, et al. Surgical removal of a choroid plexus oncocytoma in an adult cat. *J Small Anim Pract.* 2017; 58(10):589-592.
6. Doughty RW, Brockman D, Neiger R, McKinney L. Nasal Oncocytoma in a Domestic Shorthair Cat. *Vet Pathol*. 2006; 43:751-754.
7. Gulcubuk A, Erdogan O, Bozkurt ER, Gurel A, Arıkan N, Cat H. Case Report: Compact Cellular (Solid) Carcinoma Containing Hurthle Cell Areas in the Thyroid Gland of a Dog. *Revue de Médecine Vétérinaire.* 2013; 164(10). n.d.
8. Hassan BB, Altstadt A, Dirksen WP, Elshafae SM, Rosol TJ. Canine Thyroid Cancer: Molecular Characterization and Cell Line Growth in Nude Mice. *Vet Path.* 2020;57(2):227-240.
9. Kido N, Itagaki I, Ono K, Omiya T, Matsumoto R. FOLLICULAR CELL CARCINOMA OF THE THYROID GLAND IN THREE CAPTIVE AGED RACCOON DOGS (*NYCTEREUTES PROCYONOIDES*). *J Zoo Wildl Med.* 2015;46(4):889-894.
10. Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. Sixth edition. St. Louis, Missouri: Elsevier, 2016.
11. Meuten DJ, Meuten TLK. Tumors of the Urinary System. In: Meuten DJ, ed: *Tumors in Domestic Animals.* 5th edition. Ames, IO: John Wiley & Sons, Inc. 2017; 640.

12. Munday JS, Lohr CV, Kiupel M. Tumors of the Alimentary Tract. In: Meuten DJ, ed: *Tumors in Domestic Animals.* 5th edition. Ames, IO: John Wiley & Sons, Inc. 2017; 511-512.
13. Pessina P, Castillo V, Sartore I, Borrego J, Meikle A. Semiquantitative Immunohistochemical Marker Staining and Localization in Canine Thyroid Carcinoma and Normal Thyroid Gland: Dog Thyroid Carcinoma Markers. *Vet Comp Oncol.* 2016; 14(3): e102-112.
14. Ramos-Vara JA, Miller MA, Johnson GC, Pace LW. Immunohistochemical Detection of Thyroid Transcription Factor-1, Thyroglobulin, and Calcitonin in Canine Normal, Hyperplastic, and Neoplastic Thyroid Gland. *Vet Pathol.* 2002; 39(2):480-487.
15. Soares LMC, Pereira AHB, de Campos CG, Rocha LS, dos Santos TA, Souza MA, Jark PC, Pescador CA. Histopathological and Immunohistochemical Characteristics of Thyroid Carcinoma in the Dog. *J Comp Path.* 2020; 177: 34-41.
16. Yu Y, Bovenhuis H, Wu Z, Laport K, Groenen MAM, Crooijmans Richard PMA. Deleterious Mutations in the TPO Gene Associated with Familial Thyroid Follicular Cell Carcinoma in Dutch German Longhaired Pointers. *Genes*. 2021; 12(7): 997.
17. You M, Kim Y, Woo G, et al. Nasopharyngeal oncocytoma in a cat. *J Vet DIagn Invest.* 23:391-394.

CASE III:

Signalment:
10-year-old, female, Shiba dog, *Canis lupus familiaris*.

History:
In echo examination at regular checkup, enlarged gall bladder and extrahepatic bile duct enlargement was found. Computed tomography revealed a 1cm-sized mass proximal to the common bile duct. The mass was surgically removed by blunt dissection.

Gross Pathology:
The rounded mass had about 1 cm in diameter, well defined, with a firm consistency and a red brown color.

Laboratory Results:
No findings reported.

Microscopic Description:
A tumor formed beneath the luminal epithelium of the common bile duct. Tumor cells formed continuously from small diverticula and invaginations of the mucosa beneath luminal epithelium of the common bile duct. A partial demarcated, encapsulated, and infil trative tumor composed of nests, cords, acinar, and trabecular of epithelial cells supported by fibrovascular stroma. The tumor cells were polygonal, round to small spindle with distinct cell borders. Cells have moderate amounts of a finely granular, lightly eosinophilic cytoplasm, and round to oval, basilar nuclei with finely stippled chromatin and one small nucleolus. Mitoses were rare (2 per 10 HPF, 400X magnification). There was vascular invasion, but no evidence of necrosis.

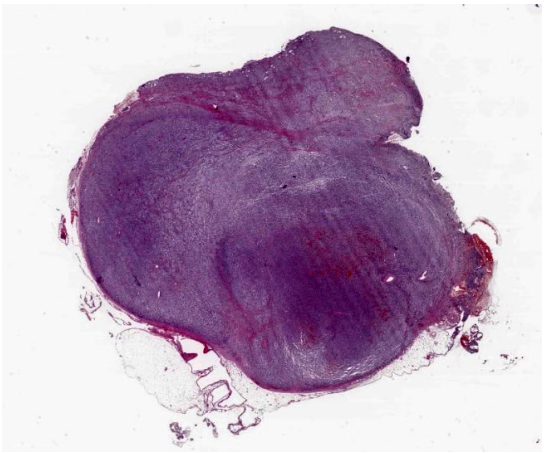

Figure 3-1. Extrahepatic bile duct, dog. One section of a nodular mass arising from an extrahepatic bile duct is submitted for examination. (HE, 6X)

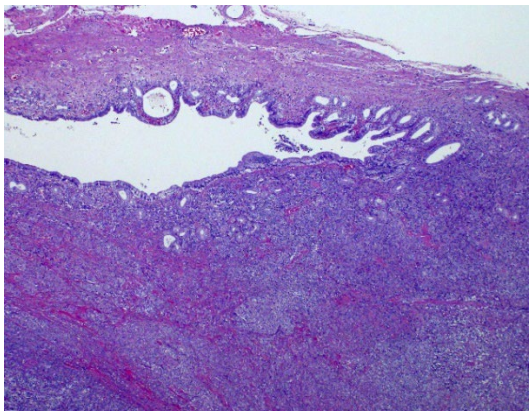

Figure 3-2. Extrahepatic bile duct, dog. The neoplasm arises from the mucosa of the bile duct and effaces the wall. (HE, 40X) (Photo courtesy of: S Laboratory of Pathology Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotohge-cho, Hirakata, Osaka, Japan)

Immunohistochemical investigation showed tumor cells strongly positive for neuroendocrine markers (synaptophysin, Insulinoma-associated1(INSM1)) and cytokeratin (AE1/AE3, CK19). Chromogranin A was negative.

Contributor's Morphologic Diagnoses:
Extrahepatic bile duct: Carcinoid (neuroendocrine tumor)

Contributor's Comment:
Carcinoid tumors are thought to arise from embryonal neural crest cells, or so-called argentaffin cells (Kulchitsky cells), which migrate to sites within the respiratory and gastrointestinal tracts during neonatal development. Most cases of neuroendocrine tumors have been reported in the gastrointestinal tract, the respiratory tract, liver, pancreas, and central or peripheral nervous system. It has also been confirmed to occur in the skin. In humans, extrahepatic bile duct carcinoid is extremely rare and accounts for 0.1-0.21% of all carcinoids of the gastrointestinal tract, with most reported cases arising from within

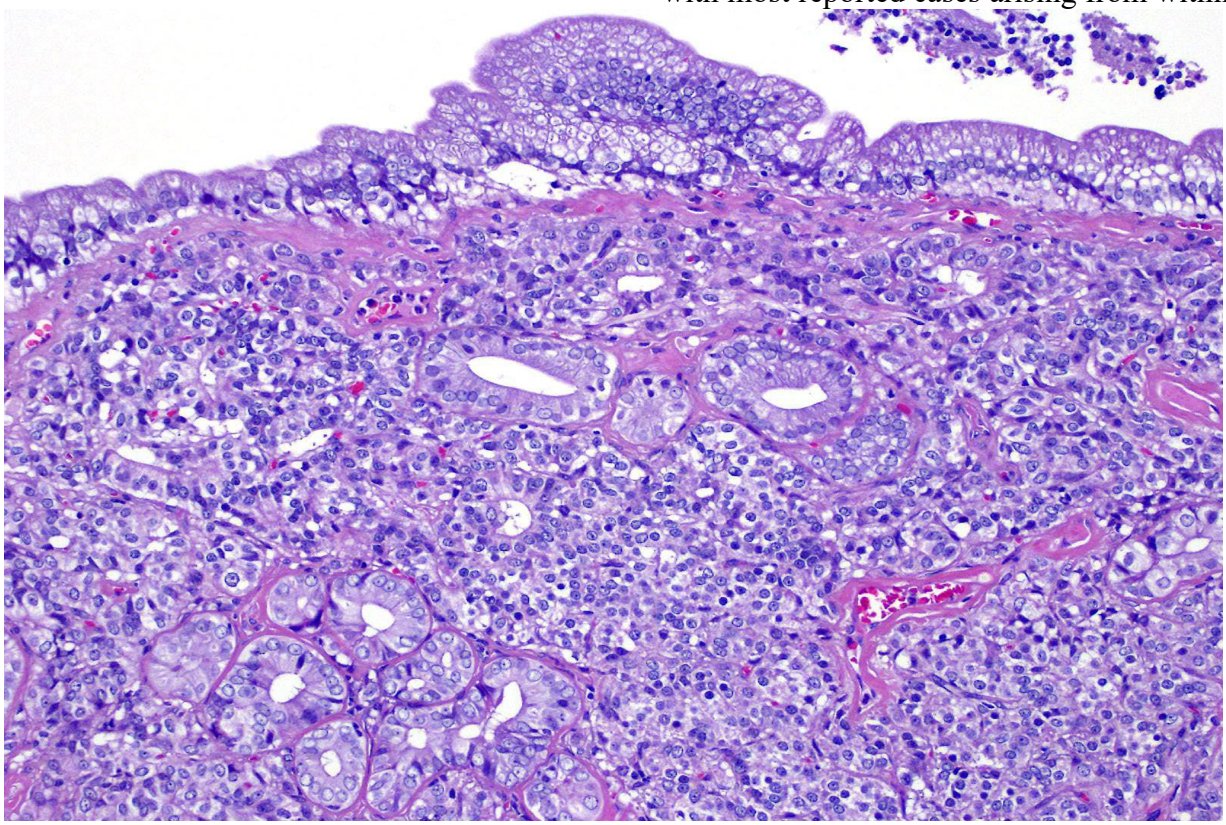

Figure 3-3. Extrahepatic bile duct, dog. Glands within the mucosa are surrounded and separated by nests of neoplastic cells. (HE, 40X) (Photo courtesy of: S Laboratory of Pathology Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotohge-cho, Hirakata, Osaka, Japan)

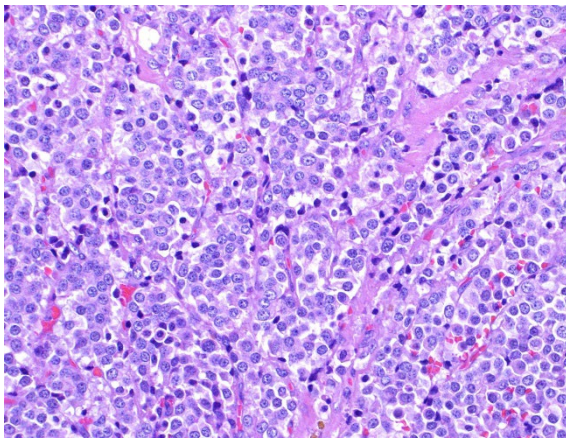

Figure 3-4. Extrahepatic bile duct, dog. High magnification of neoplastic cells. (HE, 40X) (Photo courtesy of: S Laboratory of Pathology Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotohge-cho, Hirakata, Osaka, Japan)

the gallbladder.[1,5] In domestic animals, primary gallbladder neuroendocrine carcinomas of cats, dog, and cow are reported in only a few cases[2,6,8] To the best of our knowledge, there are no reports of primary extrahepatic bile duct carcinoid in dogs.

An important differential diagnosis was cholangiocarcinoma and metastatic tumor. The definitive diagnosis of neuroendocrine tumor is based on histologic features associated with immunohistochemical staining. A relevant panel including chromogranin A, synaptophysin and NSE is recommended to diagnose hepatic carcinoid.[1,5] Recently, INSM1 was identified as a useful specific marker of neuroendocrine differentiation in neuroendocrine neoplasms. The immunoreactivity for INSM1 is greater than conventional cytoplasmic NE markers (chromogranin A, synaptophysin).[1,5] In this case, as INSM1 was strongly diffusely positive. Thus, the morphology of this tumor and the positivity of synaptophysin and INSM1 can eliminate cholangiocarcinoma. Direct infiltration by peripheral organs like liver, pancreas and small intestine or metastasis from other organs was eliminated as a possible diagnosis by no adhesion with surrounding organs and by the gross and morphologic characteristics of the tumor.

The clinicopathologic spectrum of neuroendocrine tumors ranges from the benign carcinoid to the aggressive neuroendocrine carcinoma.[1,5] The malignancy of neuroendocrine tumors is based on the following: 1) tumor size (>2 cm), 2) invasion into adjacent tissues, 3) invasion beyond the submucosa and into adjacent tissues, 4) presence of necrosis, 5) overt cell atypia with more than two mitotic cells per 10 high-power fields, 6) hormone expression and loss of chromogen immunoreactivity, and 7) nuclear P53 protein accumulation. [1,5] However, biologic behavior of neuroendocrine tumor is difficult to predict on histological features, since anaplastic features and mitotic counts are not reliable to determine the malignancy grade. The evidence of tumor invasion into adjacent tissue could reflect criteria of malignancy. So, it is recommended to consider these tumors as potentially malignant. Hepatic carcinoid has been described as aggressive tumor associated with a common metastatic potential to the peritoneum and draining lymph nodes, however it is suggested that in case of gallbladder carcinoid without evidence of intraperitoneal or distant metastasis, the prognosis is considered as good after a surgical treatment. In this case, carcinoid originated in

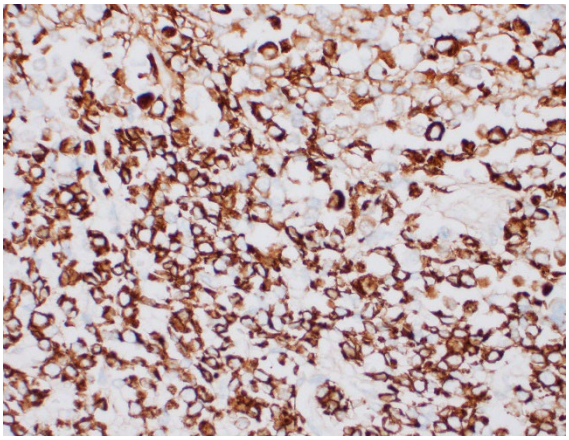

Figure 3-5. Extrahepatic bile duct, dog. Neoplastic cells demonstrate strong cytoplasmic immunoreactivity for cytokeratin. (AE1/AE3, 400X)

extrahepatic bile duct has not been reported previously in dog, so its biological behavior is unknown.

Contributing Institution:
Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University,
45-1 Nagaotohge-cho, Hirakata, Osaka 573-0101, Japan

JPC Diagnosis:
Bile duct: Neuroendocrine tumor (carcinoid).

JPC Comment:
Neuroendocrine tumors were first described in 1907 by Siegfried Oberndorfer, a pathologist at the University of Munich.[3] He coined the term "Karzinoide Tumor" (car cinoid) to describe a special cancer of the gastrointestinal system that was typically benign and not related to an adenocarcinoma.[3] Subsequent work throughout the 20th century revealed the neuroendocrine nature of the cells, which were ultimately determined to be entodermal in origin.[3] It is now recognized that neuroendocrine tumors, though they may have similar immunohistochemical staining properties, are diverse in their morphology, biologic behavior, and hormone content. [3]

A recent study described the features of gall bladder neuroendocrine tumors in 13 dogs.

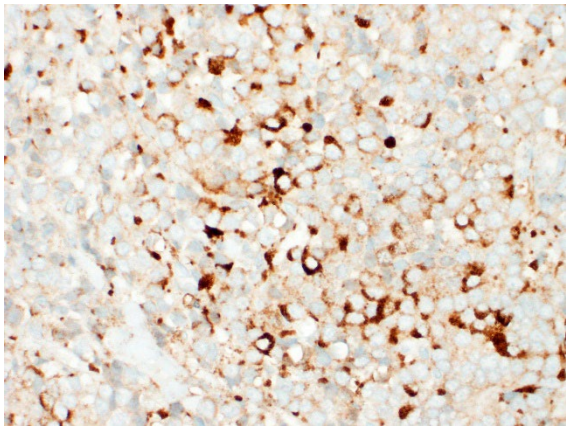

Figure 3-6. Extrahepatic bile duct, dog. Neoplastic cells demonstrate strong scattered cytoplasmic immunoreactivity for chromogranin A. (anti-chromagranin A, 400X)

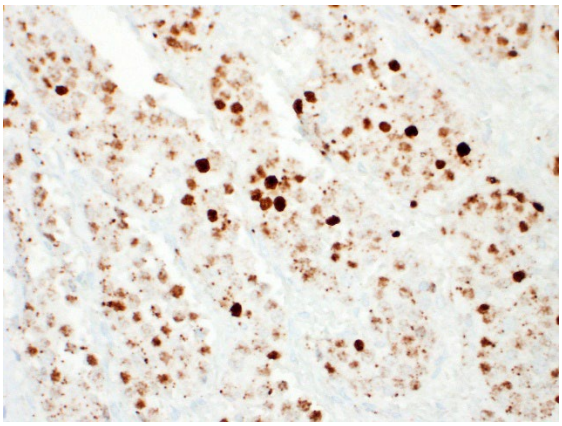

Figure 3-7. Extrahepatic bile duct, dog. Neoplastic cells demonstrate strong scattered cytoplasmic immunoreactivity for INSM-1. (anti-INSM-1400X)

Brachycephalic breeds, particularly the Boston terrier, were overrepresented, and the most common presenting complaint was vomiting.[7] Six of the animals had evidence of metastasis to the liver, with two others metastasizing to the lung and one to the mesentery.[7] Eight animals had vascular invasion, but the vast majority (12) were removed with clean margins.[7] The median survival time for the eight patients which died prior to the end of the study was 3.7 years, and the cause of death in 5 of those patients was neuroendocrine carcinoma. [7]

In contrast to the fair to good prognosis implied in the previous report of gall bladder neuroendocrine tumors, hepatic neuroendocrine tumors appear to have a very poor prognosis, with a median survival time of 3 days in one study of 10 dogs.[8] Hepatic carcinoids typically affect all liver lobes, and in one study from 1981, 14 of 15 cases metastasized, with 13 cases resulting in carcinomatosis and 14 cases of lymph node metastasis.[8,9] These findings indicate that hepatic neuroendocrine carcinomas are potentially aggressive neoplasms.

Another recent study demonstrated that neuroendocrine carcinomas are the most common gastric neoplasm in bearded dragons, ac-

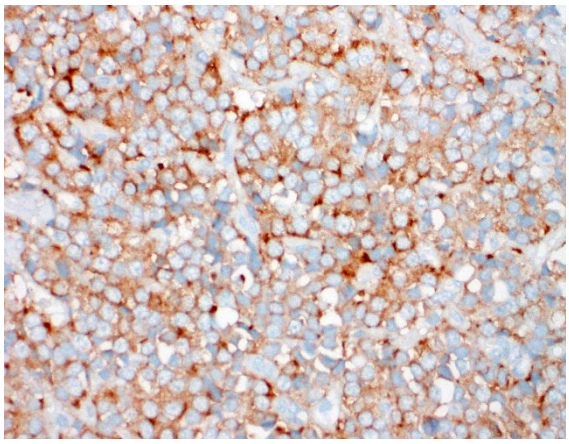

Figure 3-8. Extrahepatic bile duct, dog. Neoplastic cells demonstrate strong scattered cytoplasmic immunoreactivity for synaptophysin. (anti-synaptophysin, 400X)

counting for 16 of 26 gastric and 51 total gastrointestinal tract neoplasms.[4] In an earlier study on bearded dragons, the most common clinical sign was anorexia, and somatostatin was the only immunohistochemical marker expressed in the neoplasms, suggesting they are somatostatinomas.[10] In 6 of 10 of these cases, metastasis occurred to other abdominal organs, and 1 metastasized to the lung, indicating aggressive behavior in this species as well.[10]

References:

1. Fujino K, Yasufuku K, Kudoh S, et al. INSM1 is the best marker for the diagnosis of neuroendocrine tumors: comparison with CGA, SYP and CD56. *Int J Clin Exp Pathol* 2017;10**:** 5393-5405.
2. Johnson LK, Nunez A, Bracegirdle JR, Dwyer JR, Konold T. Neuroendocrine carcinoma of the liver and gallbladder in a cow. *J Comp Pathol*. 2008;138**:** 165-168
3. Kloppel G. Oberndorfer and His Successers: From Carcinoid to Neuroendocrine Carcinoma. *Endocr Pathol*. 2007; 18: 141-144.
4. LaDouceur EB, Argue A, Garner MM. Alimentary Tract Neoplasia in Captive Bearded Dragons (Pogona spp). *J Comp Pathol*. 2022; 194: 28-33.
5. McHugh KE, Mukhopadhyay S, Doxtader EE, Lanigan C, Allende DS. INSM1 Is a Highly Specific Marker of Neuroendocrine Differentiation in Primary Neoplasms of the Gastrointestinal Tract, Appendix, and Pancreas. *Am J Clin Pathol*. 2020;153**:** 811-820.
6. Morrell CN, Volk MV, Mankowski JL. A carcinoid tumor in the gallbladder of a dog. *Vet Pathol*. 2002;39**:** 756-758.
7. O'Brien KM, Bankoff BJ, Rosenstein PK et al. Clinical, histopathologic, and immunohistochemical features of 13 cases of canine gallbladder neuroendocrine carcinoma. *Jour Vet Diag Invest*. 2021; 33(2): 294-299.
8. Patnaik AK, Lieberman PH, Erlandson RA, Antonescu C. Hepatobiliary neuroendocrine carcinoma in cats: a clinicopathologic, immunohistochemical, and ultrastructural study of 17 cases. *Vet Pathol*. 2005;42**:** 331-337.
9. Patnaik AK, Newman SJ, Scase T, et al. Canine Hepatic Neuroendocrine Carcinoma: An Immunohistochemical and Electron Microscopic Study. *Vet Pathol.* 2005; 42:140-146.
10. Ritter JM, Garner MM, Chilton JA, Jacobson ER, Kiupel M. Gastric Neuroendocrine Carcinomas in Bearded Dragons (*Pogona vitticeps*). *Vet Pathol*. 2009; 46:1109-1116.

CASE IV:

Signalment:
9-year-old, male castrated, Shepherd Mix dog (*Canis lupus familiaris*)

History:
Presented to the hospital with a history of lethargy, decreased appetite, unwilling to walk and vomiting. The patient was alert, responsive and with cold distal extremities. On physical examination, the temperature was

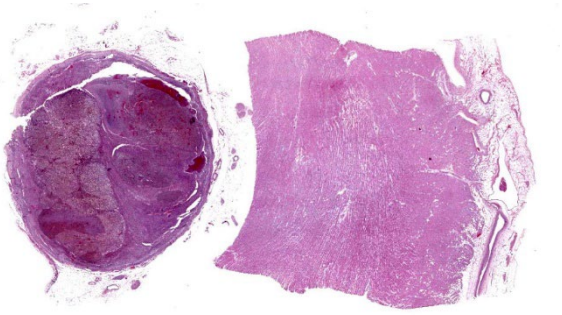

Figure 4-1. Adrenal gland and heart, dog. At subgross magnification, a neoplasm has effaced normal architecture of the adrenal gland. Myocardial fibrosis is also visible at this magnification. (HE, 5X)

97.0 F, heart rate was 76 beats/min and respiratory rate was 56 breaths/min. Left ventricle not contracting appropriately and an enlarged left adrenal gland extending into the phrenicoabdominal vein were identified on ultrasound. In addition, the patient had muffled heart sounds and weak femoral pulses.

Gross Pathology:
The right atrium and the right ventricle had multiple linear, flat dark red 2-cm to 4-cm long streaks around multiple blood vessels. The right and left free ventricular wall ratio was 1:3, and the heart weighed 472-g, which was 1.23% of the body weight (normal range in adult dog is 0.7-1.2%).

The left adrenal gland was enlarged (3.2-cm x 2.5-cm x 1.6-cm), multinodular, and firm. On cut surface, the corticomedullary ratio was 1:10 with a red to dark red, 2.5-cm in diameter mass expanding and replacing the medullary and markedly compressing the cortex. This adrenal gland was firmly attached and penetrated to the adjacent caudal vena cava. The affected caudal vena cava was segmentally and extensively dilated and completely occluded by a dark red, 3.5-cm x 1.5-cm x 1.2-cm cylindrical, firm tumor embolus firmly attached to the vascular intima. The right adrenal gland was 2.5-cm x 1-cm x 0.5-cm, with a distinct corticomedullary junction, yet medulla expanded by ill-defined light brown nodules.

Laboratory Results:
No findings reported.

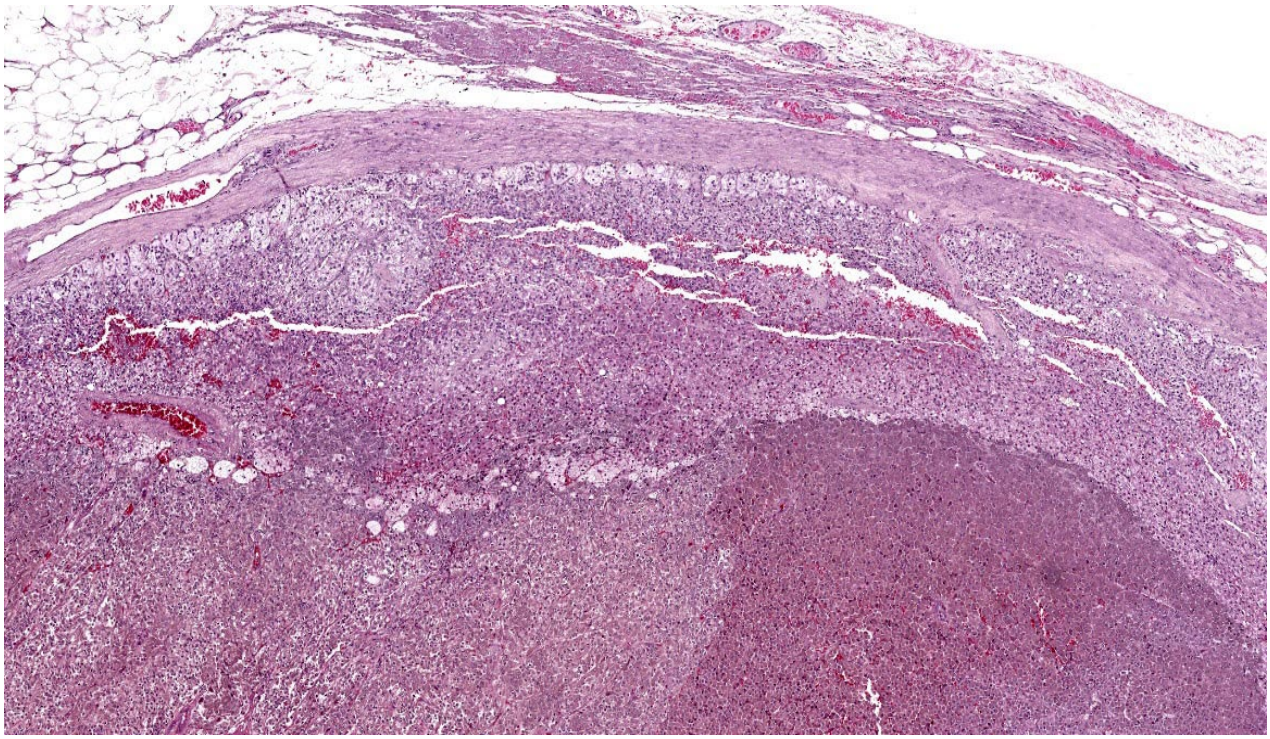

Figure 4-2. Adrenal gland, dog. The adrenal cortex is compressed by an expansile medullary tumor. (HE, 55X)

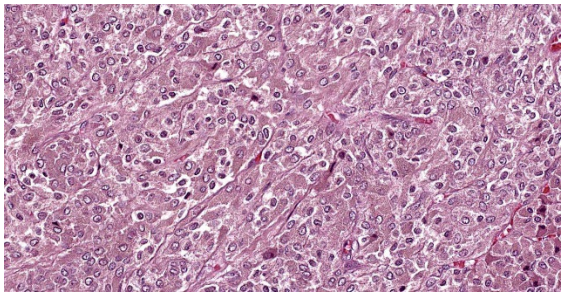

Figure 4-3. Adrenal gland, dog. High magnification of neoplastic cells from the adrenal medulla. (HE, 381X)

Microscopic Description:
Left adrenal gland (not included in this submission's slide): Markedly effacing and expanding the medulla and compressing the cortex is a nonencapsulated, infiltrative, highly cellular neoplasm, composed of round to polygonal cells arranged in dense sheets, nests and packets, supported by delicate fibrovascular stroma. There are extensive areas of necrosis, hemorrhage, fibrin and moderate numbers of degenerate neutrophils along with large clusters of neoplastic cells that invade the caudal vena cava wall and form an intravascular tumor cell thrombus. The neoplastic cells have distinct cell borders, moderate amounts of faintly granular cytoplasm, and a round to oval nucleus with finely stippled chromatin and 1-2 nucleoli. Anisocytosis and anisokaryosis are mild and there are 5 mitotic figures in ten 400x fields (2.37 mm-2). The associated celiac ganglion is focally infiltrated by lymphocytes and plasma cells.

Right adrenal gland (included in this submission's slide): Markedly expanding the medulla and compressing the cortex are multifocal to coalescing nodules comprised by neoplastic cells with similar arrangement and cytonuclear features as those described in the left adrenal gland.

Heart: Diffusely, the myocardial interstitium of the left ventricle is mildly expanded by edema and mildly increased numbers of fibrocytes and fibroblasts. Multifocally, individualized or clusters of cardiomyocytes exhibit pale sarcoplasm (degeneration) or bright eosinophilic sarcoplasm with loss of cross striations and fragmentation, and a pyknotic or karyolytic nucleus (necrosis). Often adjacent to or surrounding these myocytes are infiltrates of histiocytes and rare lymphocytes. Within patchy regions of denser fibrosis, myocytes are separated and atrophied. The tunicas media and adventitia of the multiple epicardial branches of the coronary artery are circumferentially expanded and effaced by hyalinized eosinophilic material (fibrin), and hemorrhage accompanied by perivascular edema and infiltrates of moderate numbers of macrophages, plasma cells and nuclear debris. Occasionally, the blood vessels have plump medial smooth muscle cells and endothelium.

Contributor's Morphologic Diagnoses:
Adrenal glands: Bilateral adrenal pheochromocytomas with caudal vena cava invasion

Heart: Moderate, multifocal, myocardial degeneration and necrosis with coronary arterial fibrinoid necrosis

Contributor's Comment:
Pheochromocytoma is the most common neoplasm of the canine adrenal medulla, arising from chromaffin cells, which physiologically

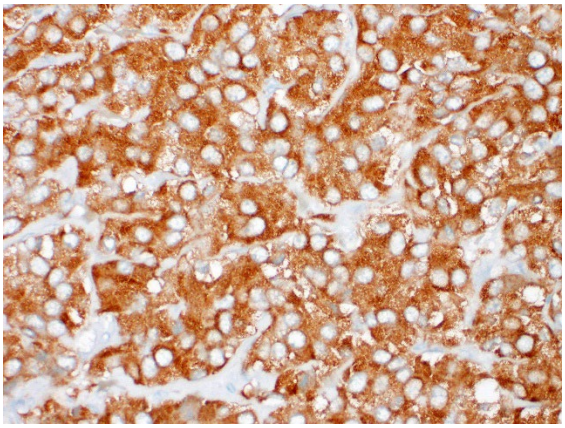

Figure 4-4. Adrenal gland, dog. Neoplastic cells demonstrate strong cytoplasmic immunoreactivity for chromogranin A. (anti-chromagranin A, 400X)

release catecholamines.[3,7,10] Although pheochromocytomas are generally unilateral, they can involve both adrenal glands. These tumors can be benign or malignant, the latter associated with invasion beyond its capsule and, in some instances, to the vena cava and/or phrenicoabdomminal vein as well as adjacent vessels. Metastasis to lung, spleen, liver, heart, bone or regional lymph nodes can also occur.[14] Pheochromocytomas can be nonfunctional or functional. Those tumors with functional activity can secrete catecholamines, being norepinephrine the most frequently reported.[6]

Catecholamines include epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine.[12] These amines are synthesized from the amino acid tyrosine, which are derived from food or formed from phenylalanine in the liver. Acting as postsynaptic neurons, chromaffin cells release secretory products when triggered by nerve impulses carried by the sympathetic fibers. The secretory products then bind to the G-protein coupled receptors located on targeted organs. Two broad receptor classifications, α and β, have been described, and they can further expand into nine receptor subtypes. Both epinephrine and norepinephrine can bind and act on adrenergic α and β receptors. The catecholamines have a profound physiology effect on blood

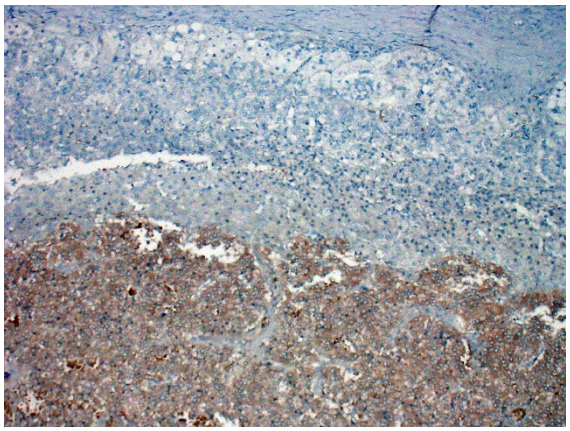

Figure 4-5. Adrenal gland, dog. Neoplastic cells demonstrate strong scattered cytoplasmic immunoreactivity for synaptophysin. (anti-synaptophysin, 400X)

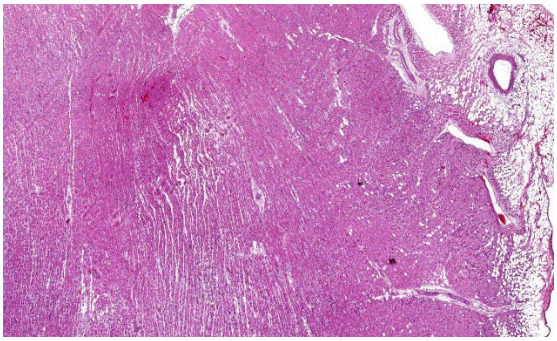

Figure 4-6. Heart, left ventricle, dog. There is diffuse interstitial fibrosis within the myocardium. (HE, 15X)

vessels and heart. Different concentration of epinephrine can elicit opposite reactions on the vasculature. At low concentration, epinephrine can lead to vasodilation by binding to β2; while at higher concentration, mainly stimulates α1 receptor and triggers vasoconstriction. In addition, increased force and rate of contraction of myocardium can occur with binding to β1 receptor.[7,12] Clinical signs are often the result of excessive catecholamine secretion from the pheochromocytoma; however, the amount of secretion is variable, sporadic and unpredictable.[7] Therefore, approximately half of the cases are incidental findings at necropsy or during surgery.

In human and animals, weakness, tachypnea, lethargy, anorexia, vomiting, high blood pressure or cardiac arrhythmias are the most frequently reported clinical signs in pheochromocytoma-affected patients.[4,12,13] Regarding myocardial changes, the theory of pheochromocytoma-associated catecholamine cardiomyopathy has been introduced.[6] However, the mechanism of the cardiomyopathy is multifactorial.[3] Myocardial injuries from circulating catecholamines have been observed in several animal models. The proposed pathogenesis of myocardial damage includes excessive stimulation of adrenergic amines that induce vasoconstriction and vasospasms in the coronary artery, leading to

myocardial hypoxia and/or infarction. In addition, the aberrant concentration of catecholamines has been shown to increase permeability of the sarcolemmal membrane and lead to increased intrasarcoplasmic calcium influx that directly causes cardiomyocyte toxic damage. Moreover, the excessive catecholamine-induced systemic hypertension as well as overloaded pressure contribute to cardiomyocyte hypertrophy and secondary hypertrophic cardiomyopathy. Histologic changes include multifocal cardiomyocyte necrosis with contraction bands, cardiomyocyte degeneration, myocardial hemorrhage, myocarditis and interstitial fibrosis.[6]

In the present case, not only similar histologic changes are present in the cardiomyocytes and interstitium, but coronary arteries exhibit vasculitis / fibrinoid change. Mechanisms leading to vasculitis and fibrinoid change are variable, including systemic hypertension, stress-induced, idiopathic, as well as primary or secondary to inflammatory responses or immune-mediated diseases.[15] No profound inflammation or immune-mediated disease were seen in this case. In addition, hyperthyroidism, diabetes mellitus and hyperaldosteronism were less likely based on clinical and pathologic examination. In cases of pheochromocytomas or hypertension, patients can have adaptive mural thickening, arteriolosclerosis or fibrinoid necrosis in heart, kidney, lung or spleen.[6] It is intriguing that the vasculitis was confined to the coronary arteries in this patient, and the cause is highly suspected to be pheochromocytoma-related.

Contributing Institution:
Auburn University
166 Greene Hall
Pathobiology
College of Veterinary Medicine
Auburn, AL
36849-5519

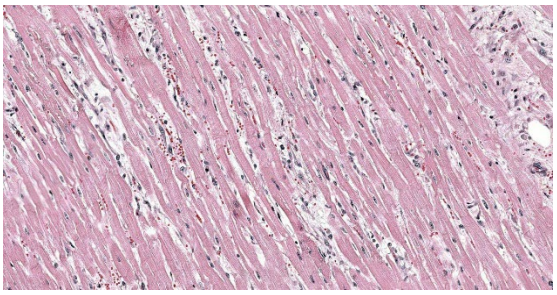

Figure 4-7. Heart, left ventricle, dog. The myocardial interstitium is expanded by loosely arranged collagen, plump fibroblasts, and there is multifocal atrophy of skeletal muscle fibers. (HE, 200X)

JPC Diagnosis:
1. Adrenal gland: Pheochromocytoma.
2. Heart: Arteriolar fibrinoid necrosis, multifocal, moderate with myocardial degeneration, loss, and fibrosis.

JPC Comment:
The contributor provides an excellent overview of adrenal pheochromocytomas and the systemic effects of excessive catecholamine production. Pheochromocytomas occur in many veterinary species, and in clouded leopards specifically they are the most common neoplasm, occurring in 1% of animals in one study of 271 animals.[16] In a separate review, pheochromocytomas accounted for 36% of reported cases of neoplasia in clouded leopards (41 of 144 cases).[9]

Other neoplasms which may originate from the adrenal medulla include neuroblastomas and ganglioneuromas, both of which are rare tumors of neuroectoderm origin.[14] Neuroblastomas originate from primitive neuroectodermal cells and can arise anywhere in the sympathetic nervous system.[1] Adrenal neuroblastomas occur in children, and are rare in dogs, ferrets, and cows.[1,2] Histologically, neuroblastomas are infiltrative, densely cellular neoplasms composed of small cells resembling lymphocytes with scant cytoplasm.[1,14] Occasionally, neoplastic cells form Homer-Wright rosettes and pseudorosettes.[1] There is limited information on the biologic behavior of this neoplasm, but in dogs, it is

likely malignant and may metastasize within the abdomen.[1]

Ganglioneuromas, on the other hand, are benign tumors which have been diagnosed in humans, dogs, cows, rats, and a cotton top tamarin.[5,8,11] The neoplasms are composed of ganglia cells admixed with satellite cells and Schwann cells in a neurofibrillary matrix with prominent fibrous connective tissue.[11,14] The ganglion cells have significant anisocytosis, abundant finely granular cytoplasm, and large round heterochromatic nuclei.[11] Occasionally, ganglioneuromas occur alongside pheochromocytomas, and in one study of rats, all 9 ganglioneuromas were associated with pheochromocytomas.[11]

References:

1. Arenas-Gamboa AM, Tanabe M, Edwards J, Storts R. Peripheral Neuroblastomas in Dogs: A Case Series. *J Comp Path.* 2014; 150: 361-365.
2. Bakthavatchalu V, Muthupalani S, Marini RP, Fox JG. Endocrinopathy and Aging in Ferrets. *Vet Pathol*. 2016; 53(2): 349-365.
3. Barthez PY, Marks SL, Woo J, Feldman EC, Matteucci M. Pheochromocytoma in dogs: 61 cases (1984-1995). *J Vet Intern Med*. 1997:11(5):272-278.
4. Dagartzikas MI, Sprague K, Carter G, Tobias JD. Cerebrovascular event, dilated cardiomyopathy, and pheochromocytoma. *Pediatr Emerg Care*. 2002 Feb;18(1):33-5.
5. Dias JLC, Montali RJ, Strandberg JD, Johnson LK, Wolff MJ. Endocrine neoplasia in New World primates. *J Med Primatol*. 1996; 25: 34-41.
6. Edmondson EF, Bright JM, Halsey CH, Ehrhart EJ. Pathologic and cardiovascular characterization of pheochromocytoma-associated cardiomyopathy in dogs. *Vet Pathol.* 2015;52(2):338-343.
7. Feldman E, Nelson R. Pheochromocytoma and multiple endocrine neoplasia. In: *Canine and Feline Endocrinology and Reproduction.* 3rd ed. Philadelphia, PA: WB Saunders;2003:440-463.
8. Grossi AB. Leifsson PS. Jensen HE. Vainer B. Iburg T. Histologic and Immunohistochemical Classification of 41 Bovine Adrenal Gland Neoplasms. *Vet Pathol*. 2012; 534-542.
9. Mathieu A, Garner MM. A Retrospective Study of Neoplasia in Non-domestic Felids in Human Care, with a Comparative Literature Review. *J Zoo Wildl Med.* 2021; 52(2): 413-426.
10. Miller MA. Endocrine system. In: Zachary JF, ed. *Pathologic Basis of Veterinary Disease*. 6th ed. St. Louis, MO: Elsevier; 2017:709.
11. Pace V, Perentes E, Germann PG. Pheochromocytomas and Ganglioneuromas in the Aging Rat: Morphological and Immunohistochemical Characterization. *Tox Pathol.* 2002; 30(4):492-500.
12. Reusch CE. Pheochromocytoma and multiple endocrine neoplasia. In: Scott-Moncrieff, CR, ed. *Canine and Feline Endocrinology*. 4th ed. Saunders; 2015: 521-551.
13. Rosol TJ, Grone A. Endocrine glands. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol. 3. 6th ed. St. Louis, MO: Elsevier; 2016:343-344, 349-352.
14. Rosol TJ, Meuten DJ. Tumors of the endocrine glands. In: Meuten DJ, ed. *Tumors in Domestic Animals.* Ames, IA: John Wiley and Sons, Inc.; 2017:787-791.
15. Stone JR. Diseases of small and medium-sized blood vessels. In: Buja LM, ed. *Cardiovascular Pathology*. 4th ed. Academic press; 2016: 125-168.
16. Thorel M, Pignon C, Arne P, Donnelly TM, Riviere J. Clouded Leopard (*Neofilis nebulosa*) Morbidity and Mortality in

Captive-Bred Populations: A Comprehensive Retrospective Study of Medical Data from 271 Individuals in European, Asian, and Australian Zoos. *J Zoo Wildl Med.* 2020; 51(1); 150-158.