2017 Northeast Veterinary Pathology Conference – Gaithersburg, MD

April 1-2, 2017

Case Submission Form

NEVPC CASE #14

IDENTIFICATION NUMBER ON SOURCE MATERIAL: 172188-16 Cornell University

INSTITUTION: Cornell University Department of Biomedical Sciences; Section of Anatomic Pathology

SIGNALMENT: 12-year-old, castrated male Labrador Retriever dog

HISTORY:

This dog presented to the referring veterinarian for a one day history of vomiting and inappetance. He has an approximately one month history of polyruria/polydipsia and elevated liver enzymes, the most recent being:

ALP 556 u/L (5-160)

ALT 359 u/L (18-121)

GGT 19 u/L (0-13)

Abdominal ultrasound revealed an approximately 2.2 cm, round, soft tissue structure extending into the lumen of the gallbladder, sharing a margin with the wall, with gravity dependent particulate matter, interpreted as precipitated bile salts, within lumen extraneous to the mass. The caudal pole of the right adrenal was enlarged, at9.7 mm in thickness, while the left adrenal was considered normal at 6.7 mm thick. The spleen was judged to be enlarged by the ultrasonographer, but no measurement was given. A large cyst was detected in the cortex of the left kidney.

Low-dose dexamethasone suppression testing yielded the following results for cortisol:

Baseline: 3.3 mcg/dL (1.0 – 6.0 mcg/dL)

4-hour post-dexamethasone: 0.8 mcg/dL

8-hour post-dexamethasone: 2.4 mcg/dL

Additionally, thyroid hormone testing yielded 1.3 mcg/dL of circulating T4 (reference range 1.0 – 4.0 mcg/dL).

GROSS FINDINGS:

Submitted to the Animal Health Diagnostic Center Section of Pathology, Cornell University, College of Veterinary Medicine were two jars. The first, labelled “liver”, contained two pieces of liver measuring 1.0 x 0.4 x 0.6 cm and 1.3 x 1.0 x 0.9 cm. The second, labelled “gallbladder”, contained a 6.2 x 4.0 x 2.6 cm gallbladder containing a blood clot and tumor within the lumen.

HISTOPATHOLOGIC FINDINGS:

GALLBLADDER (Slide 2): The gallbladder lumen is approximately 90% occluded by a large, sessile, expansile, hemorrhagic mass composed of two similar, but morphologically distinct populations of polygonal cells. The prevalent population, accounting for 75% of the cells, have moderate to abundant, lightly eosinophilic cytoplasm and large, round, prominent nuclei with finely stippled chromatin and variably distinct nucleoli. These cells are arranged in distinct packets that are separated by a thin fibrovascular stroma, compatible with neuroendocrine packeting, with moderate to severe anisocytosis and anisokaryosis. Karyomegaly is rare, accounting for less than 5% of the neoplastic population.

The minority population consists of large, polygonal cells with abundant eosinophilic to amphophilic cytoplasm arranged in a dense sheet, abruptly demarcated from the remaining population. The cytoplasm is filled with myriad, pinpoint basophilic granules, and often has conspicuous, angular cytoplasmic projections. The nuclei are centralized, round, with finely stippled chromatin and 1-2 prominent nucleoli. Mitotic figures are 7 in ten 400X fields. Anisocytosis and anisokaryosis are distinctly more severe, and karyomegaly more frequent. The gallbladder wall is diffusely dissected by hemorrhage, with small numbers of hemosiderophages scattered throughout the entire wall.

In one section of gall bladder, the mass is unapparent, and the lumen is filled with a cast of hemorrhage, necrosis, and fibrin. The mucosa in this section is thickened, with papilliferous projections into the lumen. The glands are dilated and distended with mucus exuding into the lumen.

The following immunohistochemical staining was performed on the gallbladder:

PGP9.5 (a marker for neuroendocrine cells): Approximately 50% of the major population of cells exhibits weak to moderate cytoplasmic staining. Less than 5% of the minor population exhibits weak cytoplasmic staining.

GFAP (a marker for a variety of cell types, chiefly astrocytes, ependymal cells, peritubular cells, Leydig cells, Leydig cells, human keratinocytes, osteocytes and chondrocytes, stellate cells of rat and human pancreas and liver): The tumor cells are diffusely negative.

S100 (a marker for neuroendocrine cells): The tumor cells are diffusely negative.

Neuron Specific Enolase (a marker for neuroendocrine cells): Approximately 80% of all neoplastic cells exhibit weak to moderate cytoplasmic staining.

Chromogranin (a marker for neuroendocrine cells, especially of the adrenal medulla): Approximately 50% of the major population exhibits weak to moderate cytoplasmic staining. The minor population of larger, more granular cells exhibits diffuse, strong cytoplasmic staining.

Synaptophysin (a marker for neuroendocrine cells): All neoplastic cells exhibit strong cytoplasmic staining.

The following histochemical staining was performed on the gallbladder:

Grimelius (silver stain): The neoplastic cells are diffusely positive for argyrophilic cytoplasmic granules. The minor population of large, highly granular neoplastic cells arranged in a dense, well-demarcated, nodule expresses markedly higher numbers of granules compared to the packeted, predominant population, which contain only sparse numbers of argyrophilic cytoplasmic granules.

MORPHOLOGIC DIAGNOSES:

Gallbladder: Neuroendocrine carcinoma

DISCUSSION:

Neuroendocrine carcinomas (historically called "carcinoid") are rare entities in veterinary medicine, but have been reported in dogs, cats and cattle (Patnaik, et al. 1981; Morrell, et al. 2002). They are believed to originate from the diffuse neuroendocrine system, and have been described in the gallbladder, gastrointestinal tract, biliary tract, liver, lungs, and pancreas (Patnaik, et al 1981). The biologic behavior of such neoplasms can range from benign, slow growing masses to invasive and metastatic carcinomas. In cases of gallbladder involvement, a common clinical picture encompasses signs related to extrahepatic biliary obstruction (Birettoni, et al. 2008).

In humans, the most common sites affected include the lungs and gastrointestinal tract, particularly the rectum, and there appears to be a site predilection depending on ethnicity (Yoa, et al. 2008). A study concluded that gastrin-promotion in low-grade neuroendocrine carcinomas correlated with a better prognosis (Rindi, et al. 1993).

Diagnosis is made by a combination of routine histopathologic analysis, as well as ancillary histochemical and immunohistochemical measures. On routine hematoxylin and eosin, these tumors exhibit architecture common to most neuroendocrine tumors, such as polygonal cells, variably granulated cytoplasm, dense neuroendocrine packeting, and variable rosettes. However, poorly differentiated neuroendocrine carcinomas may lose some of these features (Morrell, et al. 2002).

Histochemistry with a Grimelius stain can elucidate argyrophilic granules, which are common in these tumors (Ascoli, et al. 1986). Most of the common neurologic markers for immunohistochemistry are variably expressed by neuroendocrine carcinomas, including NSE, S100, synaptophysin, and PGP9.5. A recent study revealed that a panel of synaptophysin, NSE, and chromogranin A were the most sensitive in detecting neuroendocrine carcinomas. Additionally, electron microscopy can reveal the presence of intracytoplasmic granules (Patnaik, et al. 2005).

The chief differential diagnosis for this case was a metastatic pheochromocytoma of the adrenal medulla. These tumors exhibit very similar histologic morphology and immunhistochemical staining patterns to neuroendocrine carcinomas, indicating similar histogenesis. The finding of an enlarged adrenal gland further supported this differential. However, metastasis was not observed in other organs, and metastasis of pheochromocytomas to the gallbladder is uncommon (Barthez, et al. 1997). Serum cortisol suppression at 4 hours and escape from suppression at 8 hours is diagnostic for pituitary dependent hyperadrenocorticism. A diagnosis of gallbladder neuroendocrine carcinoma is therefore favored, but a metastatic pheochromocytoma is not implausible, and in some cases, the primary site of neuroendocrine carcinomas may be undetermined (Kuwata, et al. 2010).

The differential expression of chromogranin A and Gremelius staining, in conjunction with an abrupt transition to a cytologically distinct population within the tumor, suggests that a subpopulation of cells has arisen within the tumor. These tumor cells likely developed from the original neoplastic population, but through acquired mutations, developed into a genetically distinct sub-population.

In addition to the gallbladder, the liver was also examined histologically due to the elevation in liver enzymes, which indicated a cholestatic pattern (elevated ALP, GGT), as well as hepatocellular damage (elevated ALT). Histopathology revealed a diffuse vacuolar hepatopathy in the examined sections, with multiple, small, discrete foci of hepatocellular dysplasia. A recent study in Scottish Terriers revealed a correlation of atypical hyperadrenocorticism and elevated sex hormones with progressive vacuolar hepatopathy, dysplastic foci, and the development of hepatocellular carcinoma (Cortright, et al. 2014). In light of the low-dose dexamethasone suppression testing, this may suggest an underlying adrenal sex-steroid hormone abnormality (i.e. atypical Cushing's Disease).

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