Uncommon Endocrinopathies in Dogs and Cats - When It’s Actually the Zebra!

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Background
A small number of disorders account for approximately 90% of the endocrine diseases diagnosed in dogs and cats. For dogs, the most commonly encountered endocrinopathies are primary hypothyroidism, hyperadrenocorticism, diabetes mellitus, primary hyperparathyroidism, and paraneoplastic hypercalcemia. Hyperthyroidism and diabetes mellitus are the two main endocrine disorders of cats. However, animals have many other endocrine systems besides the adrenal, thyroid, and insulin hormone systems which may go awry. Fortunately, disorders of other endocrine systems are relatively uncommon. Unfortunately, these disorders can be diagnostically challenging to identify and can closely mirror the common endocrine and systemic disorders of the dog and the cat. In these proceedings we will explore the less common endocrinopathies of our small animal patients, with a focus on diagnosis.

Uncommon Endocrinopathies of Dogs
Insulinoma: Insulinomas are tumors of the endocrine pancreas that arise from insulin producing β cells. As such, these tumors constitutively secrete insulin. The subsequent chronic hyperinsulinemia causes a cascade of secondary clinicopathologic and clinical abnormalities, most of which relate back to chronic, severe persistent hypoglycemia. Insulinomas typically arise in older dogs (mean age 9 years) and larger dogs (>30kg); no breed predispositions are identified.

Clinical signs relate back to severe and persistent hypoglycemia. These signs include weakness, collapse after low level activity, muscle tremors, ataxia, and seizures. Seizures have a tendency to increase in frequency as the endocrinopathy becomes more longstanding. Clients may notice a pattern where clinical signs temporarily resolve after a dog eats a meal.

Diagnostically, the hallmark feature is persistent fasting hypoglycemia - typically the hypoglycemia is severe (<50 mg/dL) with many cases presenting with serum glucose < 35 mg/dL. Patients may concurrent ketosis and, if measured, fructosamine is decreased. Elevation of hepatic enzymes may also be observed if the insulinoma has metastasized to the liver. CBC and UA abnormalities are uncommonly observed.

Measurement of plasma insulin and glucose levels concurrently can confirm a diagnosis of insulinoma; a finding of hyperinsulinemia with concurrent hypoglycemia is considered definitely diagnostic for an insulinoma. Specific diagnostic thresholds are either insulin > 20 mU/l with hypoglycemia or insulin:glucose ratio of > 4.2. An alternative diagnostic approach is abdominal imaging - the presence of pancreatic and/or hepatic nodular lesions with concurrent hypoglycemia is supportive - but not definitively diagnostic - for insulinoma. The main df/dx to consider for an insulinoma are
hypoadrenocorticism, hepatic insufficiency, portosystemic shunt, improper separation of RBCs from serum, and septicemia.

The prognosis for dogs with insulinoma is unfortunately poor. The tumor has a high tendency to metastasize, with micrometastatic disease likely present in the liver and throughout the pancreas at the time of diagnosis in most patients. The median survival time with medical management is reported 2-4 months, while with concurrent surgical and medical management median survival time is 14 months. Insulinomas have been very rarely documented in cats and appear to have a similar disease course to dogs.

**Glucagonoma:** The mirror opposite of insulinomas, glucagonomas are tumors of the endocrine pancreas that arise from glucagon producing α islet cells. As such, these tumors constitutively secrete glucagon. As glucagon functions as a “starvation” phase hormone, clinical and clinicopathologic abnormalities relate back to persistent hyperglycemia and hypoaminoacidemia. Based upon reported cases, dogs with glucagonomas appear to be older (>7 years) and no breed or sex predilection has yet to be identified. Clinical signs are highly variable and may include lethargy, progressive weight loss, polyuria, and polydipsia. A small subset of patients develop a severe generalized dermatologic disease called **superficial necrolytic dermatitis.** This dermatopathy manifests as multiple erythematous and ulcerative skin lesions, often with lesions clustered around the footpads, face, mucocutaneous junctions, and ventral abdomen. Skin biopsy is needed to confirm this dermatopathy. However, the presence of **superficial necrolytic dermatitis** is strongly suggestive of a glucagonoma, but has been documented with hepatic disorders.

The most frequently observed clinicopathologic abnormality is **hyperglycemia** due to the activities of glucagon. Patients may also have non-regenerative mild anemia, elevated hepatic enzymes, hypoalbuminemia, hypolipidemia, glucosuria, and isosthenuria. **Chronically elevated glucagon can induce a secondary diabetes mellitus,** so patients with advanced disease can have a clinical and clinicopathologic picture mirroring traditional diabetes mellitus.

Measurement of **fasting serum glucagon, glucose, and amino acid concentrations** can help confirm a diagnosis of glucagonoma. **Elevated glucagon** with concurrent **hyperglycemia or hypoaminoacidemia** is considered strongly supportive of the diagnosis. Abdominal imaging may also help support a diagnosis - identification of pancreatic lesions with appropriate clinical and clinicopathologic abnormalities is strongly supportive. The main df/dx for a glucagonoma are primary diabetes mellitus, hyperadrenocorticism, and pheochromocytoma.

The prognosis for dogs with glucagonoma is poor. Surgical intervention is typically not curative due to micrometastatic disease and few medical management options are present. Reported survival times following diagnosis are <1 year.

**Pheochromocytoma:** Pheochromocytomas are functional tumors of the adrenal gland which arise from the catecholamine producing cells of the adrenal medulla. These tumors over secrete catecholamines,
typically epinephrine and norepinephrine. While encountered mostly in dogs, these tumors have also
been documented in cats. These tumors typically arise in middle-to-older age dogs and breed
predispositions have not been identified.

Clinical signs relate back to constitutive or episodic release of catecholamines from the tumors and
include atypical excitation, panting, collapse, weight loss, tachycardia, tachypnea, and rarely
polydipsia/polyuria. Patients are commonly hypertensive on serial blood pressure measurements. The
most common clinicopathologic finding is hyperglycemia but may also have elevated liver enzymes, mild
non-regenerative anemia, and proteinuria.

Measurement of the metabolites of epinephrine and norepinephrine, called metanephrines, in blood or
urine can help confirm a pheochromocytoma. Elevated metanephrines in urine, and to a lesser extent
in blood, are highly supportive of a pheochromocytoma diagnosis if an adrenal tumor is concurrently
present. As such, concurrent abdominal imaging is strongly recommended. The chief df/dx are
hyperadrenocorticism, diabetes mellitus, and glucagonoma.

The prognosis for patients with pheochromocytoma is variable. Early studies suggested that these
tumors are relatively benign, but a more recent study identified that ~25% of dogs have malignant
variants that are highly metastatic. For patients with the tumor localized to the adrenal gland, surgical
removal of the adrenal gland is considered curative. As for patients with metastatic disease, survival
duration with medical management can be varied with reports of patients living from a few months to
years.

Paraneoplastic Hypercalcemia due to PTHrp Secreting Tumors: Neoplastic disorders are the most
common cause of hypercalcemia in dogs. The two most common causes of neoplastic hypercalcemia
are primary hyperparathyroidism and humoral hypercalcemia of malignancy. In primary
hyperparathyroidism, a parathyroid tumor over secretes parathyroid hormone (PTH). In humoral
hypercalcemia of malignancy, tumors secrete PTH related peptide (PTHrp) - the vast majority of these
cases are either dogs with T-cell lymphoma or apocrine gland anal sac adenocarcinoma. Primary
hyperparathyroidism and hypercalcemia of malignancy can be differentiated by measuring PTH and
PTHrp in the face of concurrent hypercalcemia. Elevated or normal PTH is diagnostic for primary
hyperparathyroidism while decreased PTH and elevated PTHrp is diagnostic for humoral hypercalcemia
of malignancy.

For humoral hypercalcemia of malignancy, infrequently other tumors besides lymphoma and apocrine
gland anal sac adenocarcinoma can oversecrete PTHrp. The third most common tumor to secrete
PTHrp is thymoma - in fact, thymomas may account for 3-5% of humoral hypercalcemia of malignancy
cases. Additionally, PTHrp secretion has rarely been documented with solid carcinomas, including
hepatic, pulmonary, and squamous cell carcinoma. As such, if clinicians identify humoral
hypercalcemia of malignancy but cannot detect lymphoma or apocrine gland anal sac adenocarcinoma
diagnostic investigation for these less common tumors is recommended.
**Uncommon Endocrinopathies of Cats**

**Acromegaly (Hypersomatotropism):** Acromegaly results from overproduction of growth hormone (GH) from functional pituitary gland tumors in cats. This endocrinopathy most commonly arises in older cats (>8 years) and there is a predisposition for it to arise in neutered, male cats. The chronically elevated levels of GH in these cats leads to a wide array of physical changes, clinical abnormalities, and clinicopathologic arrangements.

Classic physical examination findings include overgrowth of bone structures, most notably the facial bones due to the pro-growth activity of GH. Additionally, abdominal palpation may yield enlarged abdominal viscera. The most common clinical signs are polyphagia, weight gain, gait abnormalities due to arthritis, polyuria, and polydypsia. Advanced cases may also have neurologic abnormalities due to compression of normal brain structures by their pituitary tumor.

Clinicopathologic abnormalities closely mirror **diabetes mellitus in cats.** This is because excessive GH antagonizes the activity of insulin and functionally promotes a Type II diabetes state in these patients. A such, common laboratory findings include hyperglycemia, glucosuria, hyperlipidemia, and elevated hepatic enzymes. Interestingly, these cats rarely progress into a ketoacidotic state unlike cats with true diabetes mellitus. **For clinicians, a clue a cat may have acromegaly rather than primary diabetes mellitus is if insulin therapy fails to mitigate the clinical signs and biochemical abnormalities of diabetes mellitus.**

Definitive diagnosis of acromegaly can be challenging. If available, advanced brain imaging (CT or MRI) to identify a pituitary gland tumor can be diagnostic as many of these cats have macroadenomas rather than microadenomas. Measurement of **serum insulin like growth factor,** which increases in the presence of chronically elevated GH, can also help diagnosis acromegaly. **Elevated insulin like growth factor** in the presence of appropriate clinical signs is considered diagnostic for acromegaly.

The prognosis for cats with acromegaly is variable, depending upon the relative growth and activity of their pituitary tumor. Through medical management, clinical signs can reportedly be well controlled for 1-2 years. Radiation therapy or surgical excision of the tumor can be curative, but challenging to perform. Ultimately, cats may develop uncontrollable neurologic disease as pituitary tumors enlarge.

**Hyperaldosteronism (Conn’s Syndrome):** Hyperaldosteronism results from adrenocortical tumors which over secrete aldosterone. Conceptually, the clinical and clinicopathologic features of this endocrine disorder are the mirror opposite of hypoadrenocorticism in dogs. Cats with this endocrinopathy are typically older (>10 years) and no breed or gender predisposition is identified. Clinical abnormalities relate back to the normal biological activity of aldosterone, which is increased vascular water retention and renal secretion of potassium.

The most common clinical signs are muscle weakness, cervical ventroflexion, muscle pain, ataxia, lethargy, and rarely blindness. The muscle weakness directly results from **severe hypokalemia,** the hallmark clinicopathologic finding in cats with hyperaldosteronism. Blindness, along with other neurologic abnormalities, results from severe hypertension due to high vascular volume promoted by
aldosterone. As mentioned previously, severe hypokalemia is uniformly documented in these cases - potassium values are often < 2.0 mmol/L. Serum sodium levels are typically normal however, since increased vascular water helps maintain a normal sodium concentration. Due to hypokalemic myopathy, cats also commonly elevated elevated creatine kinase and AST. Few other CBC or serum chemistry abnormalities are documented.

Measurement of serum aldosterone and renin can confirm hyperaldosteronism. Elevated aldosterone with concurrent hypokalemia or elevated aldosterone and decreased renin are functionally considered diagnostic for hyperaldosteronism. Additionally, abdominal imaging can be highly supportive diagnostically. The presence of hypokalemia with a unilateral adrenal tumor is strongly suggestive of hyperaldosteronism. The main df/dx is chronic renal failure.

Since the majority of aldosterone secreting adrenal gland tumors in cats are considered benign, surgical removal of the adrenal gland tumor can be curative for many cats. The reported survival range of cats with this endocrinopathy with surgery is 1-5 years with many cats dying due to conditions not associated with their tumor. Medical management alone can be challenging and centers on antihypertensive therapy along with oral potassium supplementation.

Hyperadrenocorticism: Similar to dogs with hyperadrenocorticism, cats may rarely develop cortisol-secreting adrenocortical tumors. Both pituitary and adrenal dependant forms are documented. Feline Cushing's is most frequently diagnosed in middle-older aged cats with a predisposition for spayed female cats. Clinical and clinicopathologic findings closely mirror canine hyperadrenocorticism, with a few key differences.

The most common clinical signs are polyphagia, polyuria, and polydypsia and less frequently alopecia and “pot belly” abdomen are reported. Unlike dogs, cats also seem to develop exceptionally fragile skin which can tear with routine handling or venipuncture. Clinicopathologic changes mirror canine Cushing's, with a stress leukogram, hyperglycemia, hyperlipidemia, elevated hepatic enzymes, isosthenuria, and glucosuria commonly documented. Unlike dogs, however, cats do not typically have marked elevations in ALP since they lack the corticosteroid induced isoform of ALP. Cats can eventually develop bloodwork abnormalities typical of diabetes mellitus since elevated cortisol can antagonize the activity of insulin. For clinicians, a clue a cat may have hyperadrenocorticism rather than primary diabetes mellitus is if insulin therapy fails to mitigate the clinical signs and biochemical abnormalities of diabetes mellitus.

Similar to the dog, the ACTH stimulation test and Dexamethasone suppression test can be used to confirm a diagnosis of hyperadrenocorticism in cats. However, both tests are not as diagnostically accurate for feline Cushing's as they are for canine Cushing's. For the ACTH stimulation test excessive stimulation, or a “positive result,” is only documented in about 50% of cats with hyperadrenocorticism; the ACTH stimulation test is performed identical to how it is performed in dogs. The dexamethasone suppression test is more diagnostically sensitive (~90%) and is performed similar to dogs. However, cats require ~10 times more dexamethasone administered than dogs (0.1mg/kg vs. 0.01 mg/kg in dogs).
Due to the higher diagnostic sensitivity, the dexamethasone suppression test is currently considered the better test for feline hyperadrenocorticism.

The long term prognosis for cats with hyperadrenocorticism is good with both effective medical management therapies for pituitary dependant hyperadrenocorticism and medical/surgical management of cats with adrenal gland tumors.