Endocrine Tumors Part I

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Endocrine tumors in domestic animals are relatively rare compared to other forms of cancer. Their effect on normal physiology, however, make their presence often very significant, even when the tumor size is small, stage is low, or invasiveness is minimal. Much of what we know about the physiology of endocrine tumors in domestic animals stems from their human counterparts. In people, endocrine tumors are most commonly diagnosed in isolation, however, several syndromes have been identified where individuals can be predisposed to multiple endocrine neoplasias. Such syndromes have been classified as multiple endocrine neoplasia I (MEM1), MEM2a and MEM2b. Similar syndromes in dogs and cats are rare but have been reported.

As with people, most dogs and cats present with one type of endocrine tumor, and the clinical signs, treatment, and prognosis varies based on the endocrine origin of the tumor itself. In this article, we will discuss the most common endocrine tumors that are observed in dogs and cats. These include tumors of the thyroid, parathyroid, endocrine pancreas, and adrenal gland. The primary focus of this discussion will be on endocrine tumors in dogs, but mention of specific entities in cats will also be made when appropriate.

Thyroid Tumors:
Thyroid tumors represent the most commonly diagnosed endocrine tumor in dogs and cats. The histology and functionality of thyroid tumors differs significantly between these species. In greater than 90% of cats, thyroid tumors are benign, functional, and often bilateral. This is in contrast to the situation in dogs where greater than 90% of these tumors are malignant, often unilateral, and non-functional. Treatment of this disease is often curative in cats whereas the prognosis is more guarded in dogs and is highly dependent on tumor stage within this species.

Thyroid tumors account for 1.1% to 3.8% of all reported tumors in dogs and the majority of these arise in the follicular cells of the thyroid gland. No identified sex predilection has been described, but certain dog breeds, including Golden Retrievers, Boxers, Beagles, and Siberian Huskies appear predisposed. Thyroid tumors in dogs are most often discovered incidentally on palpation. The thyroid glands and their associated tumors often lie just caudal to the cricoid cartilage of the larynx on either side of the trachea. Unlike in humans where the right and left lobes of the thyroid are connected by a grossly visible isthmus, the thyroid lobes in dogs are often distinct with no visible isthmus connecting the right and left lobes. Despite this lack of an apparent connectivity between lobes, bilateral thyroid tumors have been reported to occur at a relatively high frequency. Several older reports have shown that bilateral tumors can occur in 25-47% of canine thyroid carcinoma cases, but this is likely an overestimate based on more recent data. It is important to note too that thyroid tumors can arise anywhere in the cervical/thoracic inlet region as ectopic thyroid tissue can be present as cranial as the base of the tongue to the level of the heart base. This occurs as a result of cellular migration during embryologic development during the fetal stages of life. Ectopic thyroid tumors share a similar potential for invasiveness, risk for metastasis, and often lack of functionality.

A definitive diagnosis is made either by fine needle aspiration or biopsy. These tumors are typically highly vascular and should be suspected when cytology samples are contaminated with red blood cells and few to no epithelial cells. The use of ultrasound guidance is can be very helpful in obtaining a sample from less vascular portions of the mass, which will aid in obtaining a definitive diagnosis. Incisonal biopsy is rarely performed due to the risk of bleeding. In most instances, proceeding directly to surgery for complete removal after staging is recommended without biopsy.
Thyroid tumors in dogs also have a relatively high incidence of both regional (lymph node) and distant (lung) metastasis and this risk is directly correlated with size of the primary tumor. At the time of diagnosis, up to 40% of dogs will have gross metastasis and this incidence increases to nearly 100% when tumor volume exceeds 100 cm³ (i.e. a ~7.5 cm tumor). Metastasis occurs most commonly to the lungs and regional lymph nodes, including the “upstream” retropharyngeal and mandibular lymph nodes, and the “downstream” superficial cervical (prescapular) and sternal lymph nodes.

Interestingly, many dogs (up to 1/3rd of dogs in one study) presenting with thyroid tumors also have unrelated tumors elsewhere in the body. This further emphasizes the importance of complete staging of these animals during the diagnostic work up.

The typical staging for a freely movable thyroid tumor includes basic blood work (CBC, chemistry and T4), thoracic radiographs, cervical ultrasound (to evaluate both thyroid glands and regional lymph nodes) +/- abdominal ultrasound based on the relatively high risk for concurrent neoplasms in these patients. If the thyroid tumor is fixed, large, or if there is concern for significant regional invasion, CT should be utilized.

The mainstay of treatment for thyroid tumors in dogs is surgery, and the primary determinant of prognosis is tumor stage. Small, freely movable tumors that are amenable to surgical excision carry the best prognosis with median survival times of > 3 years. This generally good prognosis with surgical excision also applies to bilateral tumors. The prognosis for large (~5 cm), fixed, and/or metastatic thyroid tumors is more guarded. Contrary to many other tumors such as malignant melanoma, osteosarcoma and hemangiosarcoma, though, dogs with non-resectable or metastatic thyroid carcinomas can often still experience relatively prolonged survival times with palliative therapies alone. Reported non-surgical/palliative options for thyroid carcinomas include traditional chemotherapy (doxorubicin/platinum compounds), metronomic chemotherapy (chlorambucil), Palladia, coarsely fractionated radiation therapy, and radioactive iodine (¹³¹I). No controlled studies have been performed to prove a survival advantage with these non-surgical modalities, but observed partial and occasional complete responses in case reports make their usage a reasonable option. Of these non-surgical options, radioactive iodine therapy (¹³¹I) has shown the most promise for the durable treatment of non-surgical or metastatic thyroid carcinomas regardless of T4 functionality. In a study by Turrel et al., dogs with stage II and III disease treated with ¹³¹I had survival times in excess of 2 years and dogs with stage IV disease treated with ¹³¹I experienced a median survival of roughly 1 year. The advantage of ¹³¹I is that it can be administered systemically as a single dose, however, the disadvantage of ¹³¹I treatment in dogs is that the dose of ¹³¹I required for treatment necessitates prolonged hospitalization in isolation (days to weeks) and risk of severe, potentially fatal, bone marrow suppression is significant. Turrel et al. reported a nearly 5% mortality rate associated with ¹³¹I treatment in their cohort of dogs.

In contrast to the dog, ¹³¹I treatment has become the mainstay of treatment for cats with thyroid gland tumors with surgery rarely being recommended or performed. The quarantine times and risk of adverse events associated with ¹³¹I in cats are much lower compared to dogs.

**Parathyroid Tumors:**

Parathyroid tumors behave similarly in dogs and cats. The majority of parathyroid tumors in both species are benign and functional. Their deregulated over-production of parathyroid hormone (PTH) causes excessive reabsorption of calcium from the bone resulting in hypercalcemia. Tumors of the parathyroid glands are relatively rare but when present, the clinical signs can be dramatic. Clinical signs associated with hypercalcemia include polyuria with secondary polydipsia, lethargy, weakness, gastrointestinal upset (hyporexia, vomiting, and diarrhea), and urinary tract signs. The latter has been reported to be the most common presenting clinical problem, usually associated with urolithiasis or urinary tract infection (UTI). Urolithiasis and UTI have been reported to be present in 30% and 25% of dogs presenting with primary
hypercalcemia, respectively. These reported incidences are suspected to be higher with primary hyperparathyroidism compared to other causes of hypercalcemia (i.e. vitamin D toxicosis and hypercalcemia of malignancy) due to the often more insidious onset and longer duration of hypercalcemia in dogs with functional parathyroid tumors.

The mechanism for polyuria and thus polydipsia in hypercalcemic animals involves a reversible inability of the kidney to respond to ADH in the presence of excessive calcium concentrations. The kidney’s excessive water and electrolyte losses caused by this diabetes insipidus-like syndrome can lead to isosthenuric/hyposthenuric pre-renal azotemia as well as renal azotemia. The incidence of azotemia is much lower in cases of primary hyperparathyroidism relative to hypercalcemia of malignancy, which are reported to be 11% and 71% respectively. Risk of soft tissue mineralization is also lower with primary hyperparathyroidism as the phosphorus is often low resulting in a relatively low calcium:phosphorus product in most cases despite a high calcium. Additionally, if azotemia is present, this is reversible in the majority of cases following treatment of the underlying cause of the hypercalcemia.

The vast majority, >95%, of parathyroid tumors in dogs and cats are benign adenomas or classified as parathyroid gland hyperplasia. Adenocarcinomas make up the remaining 5%. Similar to thyroid tumors, parathyroid tumors can occur both in their normal anatomic location or can be ectopic anywhere along the cervical to cranial thoracic region. Because the majority of these tumors are small (<1cm), the diagnosis is rarely made based on palpation alone. Rather, the diagnosis often comes after hypercalcemia is identified on blood work and an inappropriately normal or high parathyroid hormone (PTH) concentration found on a paired ionized calcium:PTH test. This combination is diagnostic for primary hyperparathyroidism. Primary hyperthyroidism is the third most common cause of hypercalcemia in dogs, therefore it is essential to rule out the more common causes of hypercalcemia early in the diagnostic algorithm. It should also be noted that not uncommonly, dogs can have two causes of hypercalcemia (i.e. hypercalcemia of malignancy and primary hyperparathyroidism) so complete staging along with performing the “malignancy profile” (iCa**:PTH:PTH-related peptide) through the Michigan State University Diagnostic Lab, should be considered in every work-up for hypercalcemia. PTH and iCa** are measured from serum while PTH-rp is measured from plasma collected in an EDTA tube. These samples should also be performed on fasted animals as lipemia can cause a spurious elevation in PTH-rp.

In the hypercalcemic patient, it may be necessary to empirically treat the hypercalcemia pending test results and definitive treatment of the underlying cause of the hypercalcemia. Asymptomatic patients with a calcium:phosphorus product less than 60 often do not require interim treatment for the hypercalcemia while diagnostics and definitive management are pending. If immediate treatment is indicated, as in cases with significant clinical signs, marked Ca:P elevations, or total calcium >18mg/dL, the initial therapy for hypercalcemia is often non-specific. The most effective and least invasive initial treatment for hypercalcemia is fluid diuresis. In most cases of hypercalcemia, simple fluid diuresis can decrease serum calcium to temporarily safe concentrations to alleviate clinical signs while diagnostics are pursued. Administration of isotonic fluids such as 0.9% NaCl, Norm-R or Plasmalyte, (even LRS which contains a small amount of calcium) can be administered at 100-125mL/kg/day. Furosemide at a dose of 2-4mg/kg IV BID to TID can be added once volume expansion with crystalloids has been performed and continued until definitive treatment can occur. Electrolytes should be monitored closely during heavy diuresis, especially with 0.9% NaCl to monitor for potential hypernatremia or other electrolyte aberrations. Additional medications such as bisphosphonates, corticosteroids and calcitonin are rarely necessary in the initial treatment of hypercalcemia and are reserved for cases in which the underlying cause of the hypercalcemia if surgery is not elected. Steroids in particular should be withheld until a definitive diagnosis is obtained as these drugs can alter the ability to obtain a diagnosis in some malignancies (i.e. lymphoma, myeloma and some leukemias). The goal of initial empirical therapy should not be focused on normalizing the calcium but rather decreasing the severity of hypercalcemia until a definitive diagnosis and therapeutic plan can be established.
The treatment of choice for primary hyperparathyroidism is surgery. While the surgical procedure itself is often routine with minimal potential for intra-operative complications, the post-operative management can be finicky with potential life-threatening consequences if not managed properly. The major risk factor for potential post-operative complications is the development of clinical hypocalcemia.

The development of post-operative hypocalcemia is sporadic and difficult to predict. Some authors recommended supplementation for dogs with pre-operative total calcium concentration of $>14\text{mg/dL}$; however, this “cut-off” value has come into question since recent studies have failed to observe a correlation between pre-operative calcium concentration and incidence of post-operative hypocalcemia. In the author’s practice, no patient is started on calcitriol or calcium unless hypocalcemia is noted post-operatively or if all 4 parathyroid glands are removed. The goal of calcitriol and calcium therapy in cases of surgically treated primary hyperparathyroidism is to prevent clinical hypocalcemia, while maintaining a low-normal calcium concentration in order to promote endogenous PTH production from the remaining parathyroid glands. In cases where all 4 parathyroid glands are removed, life long supplementation with calcitriol and calcium is often required since as few as 6% of dogs possess ectopic parathyroid tissue.

The recommended initial dosage of calcitriol is 20-30ng/kg/day (note: nanograms). Additional supplementation of oral calcium carbonate is commonly combined with calcitriol but may not be required since ample calcium is obtained from most commercial canine diets. The most important supplement is calcitriol as this is required for the majority of calcium absorption in the small intestine; without calcitriol, supplemented calcium is poorly absorbed. Calcitriol is available in 0.25ug (250ng) and 0.50ug (500ng) tablets but can also be obtained from reputable compounding pharmacies. The time to effect can take 1-4 days, and thus frequent monitoring during the initial phases of therapy is important. If acute clinical hypocalcemia occurs, intravenous calcium gluconate should be utilized until the calcitriol can take effect. Calcium gluconate is administered IV to effect while monitoring the patient’s ECG, then at 5-15mg/kg/day until weaning is possible without recurrence of hypocalcemia.

Assuming the source of the excessive PTH is removed and post-operative calcium homeostasis is either managed endogenously by the patient or through proper medical management, the prognosis is excellent.

**Tumors of the Endocrine Pancreas:**

Pancreatic islet cell tumors are also relatively rare, even among other endocrine tumors. This paucity of islet cell tumors is especially true in cats. The most common type of islet cell tumor in dogs is insulinoma. Other tumor types include glucagonoma and gastrinoma (Zollinger-Ellison syndrome). Other tumors of the pancreas include exocrine pancreatic adenocarcinoma and benign nodular changes and abscess. The focus of this discussion will be on insulinoma.

Insulinoma is a malignant neuroendocrine tumor of the pancreatic $\beta$-islet cells. The $\beta$-islet cells make up ~70% of the cellular mass making up the islet of Langerhans and are responsible for the production of insulin. The remaining 30% of the islet mass is comprised of the glucagon secreting $\alpha$-cells, the somatostatin secreting $\delta$-cells and the pancreatic polypeptide-secreting F-cells. The central role of insulin within the body is regulation of blood glucose concentrations and prevention of hyperglycemia. Insulin also plays an important role in lipid synthesis and enzymatic activity. These “secondary” roles of insulin within the body likely contribute to the various paraneoplastic syndromes that can occur with this tumor type.

Canine insulinomas can occur in any breed, but are most commonly seen in medium to large breed dogs. West Highland white terriers also appear overrepresented. Insulinoma is most commonly diagnosed when an adult patient is presented with hypoglycemia in the face of a normal or elevated blood insulin concentration. Prior to being able to measure insulin directly,
insulinoma was often suspected based on the fulfillment of “Whipple’s Triad”. The triad is fulfilled when a patient was presented with clinical signs of hypoglycemia, a serum glucose of <50mg/dL was measured, and resolution of clinical signs occurred upon supplementation with exogenous glucose.

In contrast to human insulinomas where the majority of insulinomas are benign and cured with surgery, insulinomas in dogs are often malignant with a high risk of metastasis. Metastatic lesions are detected at the time of initial diagnosis or at surgery in >50% of dogs. The most common sites of metastasis include the regional lymph nodes and liver. Pulmonary metastases are very rare.

A common conundrum in the treatment planning for insulinoma is the fact that currently available imaging modalities are relatively insensitive for visualizing both the primary tumor and metastatic lesions. Ultrasound is the most common imaging modality used but lesions are missed in >50% of cases. CT is likely more sensitive but even with this modality, the correct identification of the primary tumor is still made in only 72% of cases. CT also has the issue of having a higher false positive error rate in the diagnosis of metastatic lesions.

The primary treatment for insulinoma is surgery. Based on the low sensitivity and specificity of imaging in localizing the primary tumor and identifying metastasis, exploratory laparotomy is recommended regardless of the imaging results. Unlike ultrasound and other imaging techniques, gross visualization and palpation of the pancreas at surgery allows for confirmation in the majority of cases. Within the pancreas, insulinomas are often found as a solitary, firm, and pale nodule. If a nodule is not observed, options include partial pancreatectomy with the hope that the occult mass is present within the removed sections or close the abdomen and consider medical management until an overt mass is later identified and can be removed. At surgery, it is also important to remove any enlarged lymph nodes and biopsy the liver regardless of its appearance as metastasis to the liver are not uncommonly microscopic in nature.

The primary readout for a successful surgery is normalization of the patient’s glucose following the procedure. Even in cases where gross metastatic disease is left in situ (i.e. diffuse liver metastasis) removal of the primary tumor and any additional resectable tumor burden can improve glycemic control, at least temporarily. When the disease is removed completely, the majority of dogs will normalize their glucose with or without a transient hyperglycemic phase. In rare cases, the development of diabetes mellitus can be permanent and when hyperglycemia does occur, administration of exogenous insulin should be initiated quickly to prevent diabetic ketoacidosis, cataracts and other diabetes related complications. In cases where diabetes does develop, these patients often require relatively high doses of insulin for control. Periodic monitoring of glucose should be performed following surgery to monitor for potential disease relapse/progression. Persistent hypoglycemia following surgery would suggest incomplete removal of the tumor or metastasis in which case adjuvant therapies as discussed below can be considered.

The prognosis for insulinoma is guarded. The median hypoglycemia free time for dogs treated with surgical excision alone for localized insulinoma (stage I) has been reported to exceed 14 months. With medical management alone, the median survival time is reduced to ~6 months. When surgery and medical management were combined in one study, the median survival time was found to be 1316 days. This is in contrast to when stage III disease is diagnosed, where median survival times are closer to 6 months even with surgery and medical management.

Medical management for insulinoma is multimodal and can include dietary modifications (more frequent meals), restriction of strenuous activities, and administration of various drugs that either reduce hypoglycemia by altering glucose metabolism and cellular responsiveness to insulin or by being directly cytotoxic to the insulin producing tumor cells themselves. Such medications include prednisone, diazoxide, octreotide, streptozotocin and Palladia. In the authors practice, management of such cases of persistent hypoglycemia either following surgery or when surgery
is not performed, often starts with dietary and activity management, prednisone (0.25-0.5mg/kg BID), +/- diazoxide at 5mg/kg BID and discussion of Palladia (2.75-3.25mg/kg PO EOD). In the past, the cost of octreotide was prohibitive, but now with less expensive compounding, this drug is also becoming an option. The reported dose of octreotide is 10-50ug SQ BID to TID. Streptozotocin is considered late in the treatment course by in the author’s practice due to the high risk of severe side effects and relatively equivocal benefit. When dosed in a q3 weeks schedule, there was no improvement noted in glycemic control between treated dogs and historic controls. When dosed at a q2 week interval, several dogs did show resolution of hypoglycemia (8 of 19 developed diabetes mellitus) but adverse events leading to the death or euthanasia of nearly 30% of patients occurred. Therefore, further evaluation is necessary to establish a safe dose while maintaining efficacy.