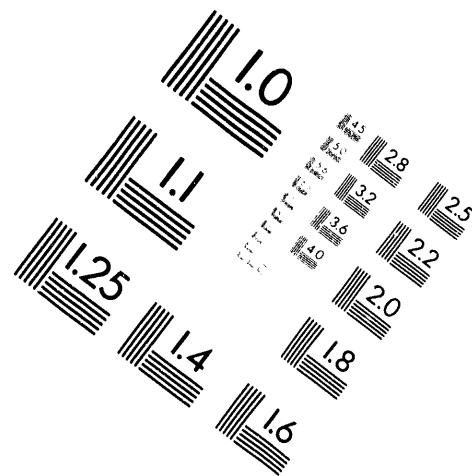
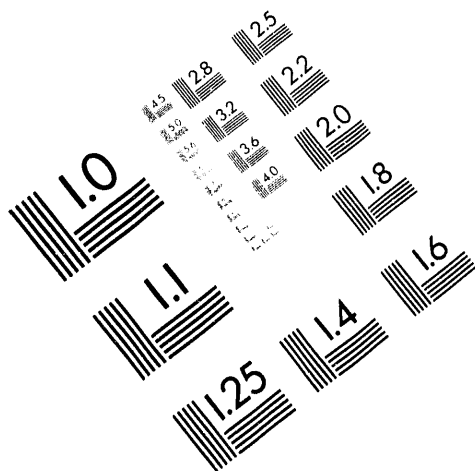




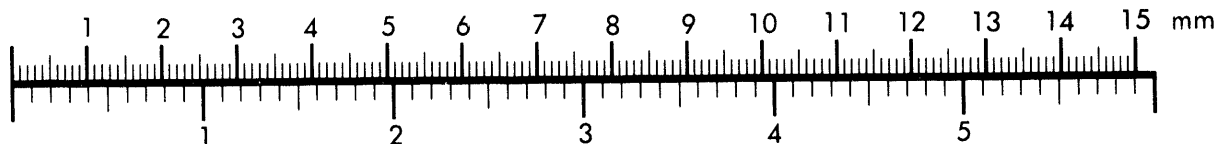
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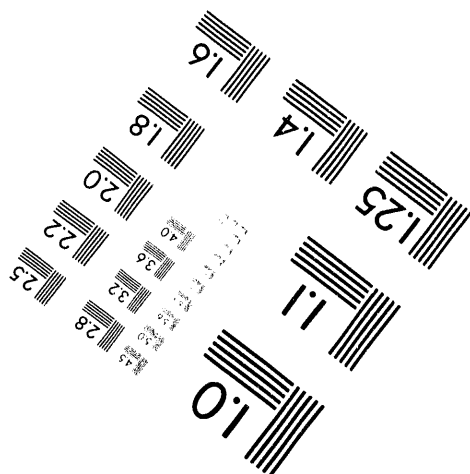
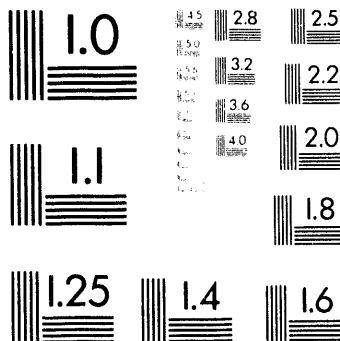
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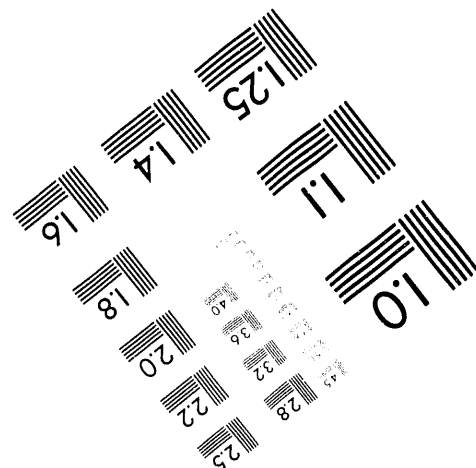
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March 1994

Presented at the
Post-Graduate Course in Veterinary Oncology
March 22-24, 1994
Santiago, Chile

Work supported by
the U.S. Department of Energy
under Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
Richland, Washington 99352

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DIAGNOSIS AND MANAGEMENT OF ENDOCRINE GLAND NEOPLASMS

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Introduction

Functional and nonfunctional neoplasms of the endocrine glands constitute some of the more challenging diagnostic and therapeutic problems in veterinary cancer medicine. They can produce a variety of clinical signs and syndromes often similar to those of other disorders. The clinical signs are usually the result of an overproduction of hormones that are normally biosynthesized by the neoplastic endocrine gland (orthoendocrine syndromes), as opposed to those that are the result of hormones (polypeptides) that are not normally biosynthesized and secreted by those cells that have undergone neoplastic transformation (paraendocrine syndromes). The latter are also referred to as endocrine paraneoplastic syndromes or ectopic hormone syndromes. Because of the physiologic potency of the hormones produced by endocrine gland neoplasms, the biological effects produced by a neoplasm may be out of proportion to the actual size of the tumor. This seminar will focus on the clinical signs and syndromes associated with neoplasms of the thyroid, adrenal, and parathyroid glands, and pancreas. Discussion will concentrate on the mechanisms producing the clinical signs, diagnosis, staging, therapy and prognosis.

THYROID GLAND

Canine

Thyroid tumors comprise approximately 1.2% of all canine neoplasms. The risk of thyroid tumors rises sharply in dogs over 6 years of age, particularly among females, though there is generally no sex predilection. Adenomas occur in dogs 7-15 years of age (mean 10.7 years), and carcinomas in dogs 4-18 years of age (mean 9 years). Boxers, Golden Retrievers, and Beagles have been reported as a high risk for thyroid neoplasia. A review of the medical records of 458 colony born beagle dogs maintained in our facilities revealed 26 cases of thyroid neoplasia resulting in an incidence of 5.6%. The pathogenesis of canine thyroid cancer is unknown, but possible causative mechanisms postulated include thyroid hyperplasia resulting in thyrotropin excess, primary hypothyroidism resulting in excess TSH stimulation, ionizing radiation, thyroiditis, and anomalous follicular patterns in brachycephalic dogs. The association of cancer risk in those breeds also considered to be at high risk for hypothyroidism suggests a possible relationship between hypothyroidism and thyroid cancer. We reviewed the medical records of 10 beagle dogs with thyroid carcinomas that had been previously diagnosed as hypothyroid by TSH-response test. The results of that evaluation showed that the median time from determination of thyroid functional status in those dogs to tumor diagnosis was 529 days (mean \pm 1SD: 771 ± 625 ; range: 258-1756). There is evidence to suggest that elevated TSH can induce TSH-dependent thyroid adenomas and finally autonomous thyroid carcinomas.

Clinical Signs and Diagnosis

Diagnosis is usually by incidental discovery of a cervical mass. The mass or masses may be located anywhere from the larynx to the thoracic inlet. Most (83-88%) thyroid neoplasms are highly malignant, with local invasion of the trachea, esophagus and blood vessels. Hematogenous metastasis to regional lymph nodes and the lungs is common. Adenomas are usually palpable as a single mass in an otherwise normal gland and are freely movable under the skin, particularly in a cranial-caudal direction. Carcinomas, on the other hand, generally grow rapidly, producing extensive local invasion that results in fixation to surrounding tissues. Associated clinical signs can include dysphagia, dyspnea, lymphedema, dysphonia, weight loss, local pain and palpable regional vessels. Approximately one-third are bilateral; two-thirds are unilateral. However, benign and malignant thyroid tumors cannot be accurately differentiated on clinical grounds alone. This was shown in one study in which 8 of 14 dogs with thyroid tumors had no clinical signs on presentation. Diagnosis usually requires procedures in addition to physical examination and evaluation of the history.

Diagnostic aids include radiography, radioisotope scanning, ultrasonography, hematologic studies and serum chemistry determinations. Cervical survey films occasionally reveal tracheal deviation and cranial mediastinal masses or calcific densities. Thoracic radiographs are useful in detecting metastatic disease or ectopic thyroid tissue. Thyroid scintiscans can be performed using ^{131}I or sodium pertechnetate. Scintiscans using ^{131}I may show diffuse accumulation or "cold" areas, with no isotope accumulation in thyroid neoplasms. Pertechnetate is visible in scintiscans of 75% of clinically detected thyroid tumors. Scintiscans may also help determine the functional status of thyroid tumors.

In human subjects with thyroid tumors, the principal value of ultrasonography is to differentiate among solid, cystic, and mixed solid-cystic nodules of the thyroid gland. The applicability of ultrasonography to diagnosis of thyroid neoplasia in dogs has not been determined but probably warrants clinical evaluation.

Measurements of serum T_4 and T_3 concentrations are rarely of help with small or unilateral tumors, since euthyroidism is usually maintained. About 22-28% of dogs with thyroid tumors exhibit hyperthyroidism due to increased serum T_4 and T_3 levels. These animals will present with $T_4 > 3.6$ ug/dl and $T_3 > 138$ ng/dl. With bilateral tumors or diffusely infiltrating carcinomas, these hormone levels may be reduced, causing signs of hypothyroidism.

Definitive diagnosis of thyroid neoplasia requires histopathologic evaluation of biopsy samples, obtained by fine-needle aspiration biopsy, needle-punch biopsy, or incisional or excisional biopsy. Fine-needle aspiration should be performed when significant conclusions may be established by evaluating the morphology of a relatively few dissociated cells. The primary advantages of fine-needle aspiration biopsy include the lack of postbiopsy complications, ease of performance, and avoidance of local or general anesthesia. Disadvantages include possible failure to obtain a representative specimen, small size of the biopsy sample, blood contamination, and necessity for biopsy interpretation by an experienced cytopathologist. Fine-needle aspiration was diagnostic in only 50% of canine thyroid carcinomas described in one study. Needle-punch biopsies have the advantage of providing the clinician with a core of tissue for histologic diagnosis and, possibly, avoiding unnecessary surgery. Disadvantages include possible tracheal puncture, hemorrhage or transient injury to the recurrent laryngeal nerve. An associated hazard is the possibility of lacerating tissues and organs that

move with respiration while attempting to sample lesions with an immobilized needle.

Excisional and incisional biopsies allow direct viewing of the affected organ or tissue and securing of a large sample that retains the morphologic characteristics of the tissue. Disadvantages include the need for general anesthesia and possibility of postoperative complications.

Staging and Prognosis

A number of factors are known to be of prognostic importance in thyroid carcinoma in humans. Among these are age, sex, histologic subtype and the extent of disease at the time of diagnosis. Similar factors may apply to thyroid carcinoma in veterinary patients. Studies in humans have shown that the TNM staging classification contributes significantly to survival, but does not include other contributory prognostic variables, whereas the prognostic index developed by the European Organization for Research on Treatment of Cancer (EORTC) thyroid study group, which takes into account age and histology, proved a reliable predictor of survival (Table 1).

Table 1 EORTC prognostic score

Age at diagnosis (yr)	
+ 10 if medullary carcinoma	
+ 45 if principle or associated cell type is anaplastic	
+ 10 if T-category is T ₃	
+ 15 in addition to above if there are multiple metastatic sites	
= Total score	Risk group
< 50	1
50-65	2
66-83	3
84-108	4
≥109	5

While neither the TMN classification nor the prognostic index has been applied to a large number of dogs with thyroid carcinoma, there is evidence to suggest that histologic pattern affects survival.

Treatment

There is not general agreement concerning treatment for thyroid neoplasia. The optimum therapy for canine thyroid carcinoma depends on many factors, including the functional status of the dog's thyroid tumor. For example, ^{131}I would be expected to be more effective in treatment of hyperfunctional thyroid tumors than less functional tumors due to the higher uptake of ^{131}I in hyperfunctional tumor tissue. Therefore, before embarking on a course of treatment with ^{131}I , an attempt should be made to determine whether an adequate radiation dose can be delivered to the cancer. In general, if the predicted radiation dose to the tumor is less than 50 to 100 Gy, alternate means of treatment should be considered. Surgical extirpation appears to be preferable when feasible, but invasive carcinomas are often inoperable; 40% of dogs reported in one study had metastases at the time of diagnosis. Complete excision early in the course of the disease, if possible offers the best prognosis. Unilateral thyroidectomy usually incurs no postoperative complications and necessitates only routine care. A serious complication of bilateral thyroidectomy is inadvertent removal of the parathyroid glands. If total parathyroidectomy cannot be avoided, postoperative observation for signs of hypocalcemia is important. Lifelong feeding of a high-calcium diet and supplemental vitamin D_3 corrects this deficit. Acute hypocalcemia during the immediate postoperative period is treated with intravenous calcium gluconate solution.

Radioactive ^{131}I can be used to treat unresectable or residual thyroid cancer if iodine uptake is demonstrated. For dogs, the therapeutic ^{131}I dosage is 1 Ci per kilogram of body weight given as a single intravenous injection and repeated in two to four months. A lack of data on long-term outcome makes it difficult to evaluate the efficacy of ^{131}I treatment in canine thyroid carcinoma. External beam radiation therapy should be considered for inoperable primary tumors or, intraoperatively, when the completeness of excision is doubtful.

Thyroid carcinoma has been treated with doxorubicin, alone or in combination with cyclophosphamide and/or vincristine. Tumor regression has been observed after such chemotherapy in a limited number of cases, suggesting that doxorubicin may be effective for treatment of dogs with residual or metastatic thyroid carcinoma.

Those animals with hyperthyroidism (thyrotoxicosis) may also require treatment with antithyroid medications to alleviate the signs of excessive thyroid hormone before and/or after treatment for the thyroid tumor has been initiated.

Until more evidence is available through prospective clinical trials, thyroid carcinoma in dogs probably warrants a poor prognosis. Exceptions may be small (<3cm), noninvasive, encapsulated tumors without evident metastasis at the time of excision. As with most canine tumors, early diagnosis and aggressive therapy probably offer the best opportunity for cure or prolonged survival.

PANCREAS

Insulinoma (Islet cell tumor, Pancreatic beta cell tumor)

Insulinoma is the most common tumor of the endocrine pancreas in the dog, accounting for approximately 0.2% of primary neoplasms in all species, according to one report. Dogs between 5 and 12 years of age are the most frequently affected; the range of incidence is from 5 to 15 years. There is no sex predilection. Though insulinoma may occur in any breed of dog, a higher incidence has been reported in Standard Poodles, Boxers, Fox Terriers, German Shepherds and Irish Setters. The majority of insulinomas (between 69 and 95%) are functional carcinomas, occurring most commonly in the right lobe (duodenal) of the pancreas. Visceral metastasis is common, particularly to regional lymph nodes and liver, and occurs early in the course of the disease, usually before clinical intervention.

Clinical Signs and Diagnosis

The functional nature of the carcinomas results in hyperinsulinism. Hyperinsulinism is a syndrome associated with inappropriate secretion of insulin by a functional insulinoma. Clinical signs result from neuroglycopenia and increased plasma catecholamine concentrations. Neuroglycopenic signs include seizures, weakness, ataxia, fasciculations, abnormal behavior, depression, polyphagia, weight gain, syncope, polydipsia/polyuria and coma. Duration of signs is highly variable, ranging from 1 day to several years. Clinical signs of polyneuropathy have been described in 4 dogs with insulinoma. The pathogenesis of polyneuropathy in these cases remains speculative. It might represent a paraneoplastic or remote effect of the tumor. People with certain malignancies, in particular, commonly have subclinical, electrophysiologic evidence of neuropathy.

Polyneuropathies have also been reported in dogs with malignant neoplasms without evidence of metastases. Recent studies suggest an underlying immunologic process in some paraneoplastic neuropathies.

Diagnosis is most often made by demonstrating inappropriately elevated concentrations of circulating insulin in the presence of hypoglycemia. A blood sample is drawn when the blood glucose level falls or is below 60 mg/dl and is submitted to the laboratory for concurrent determination of both glucose and insulin concentrations. It may be necessary to fast suspect animals for 24 or even 48 hours to achieve significant hypoglycemia.

Results of these assays can be used to calculate an appropriate ratio, demonstrating hyperinsulinism. Several ratios have been suggested as aids in confirming a diagnosis of hyperinsulinism. These include the insulin: glucose ratio, amended insulin: glucose ratio (AIGR), and glucose: insulin ratio. Though the AIGR appears to enjoy some favor in usage, there is some question regarding whether it offers any diagnostic advantage over other ratios. It is important to remember that these ratios are only another diagnostic tool and not a substitute for a complete clinical evaluation.

Provocative testing is also useful in some cases for determining the cause of fasting hypoglycemia. The intravenous glucagon tolerance test is one of the most widely used. Other tests used include intravenous glucose tolerance, oral glucose tolerance, leucine tolerance and tolbutamide tolerance tests.

Staging and Prognosis

One report describes 73 dogs with insulinoma that were staged clinically according to the staging system of the WHO (Table 2). Age and clinical stage appeared to have prognostic value.

Table 2. Staging Protocol for Insulinoma

Stage	Criteria
1	Tumor confined to pancreas
2	Tumor confined to pancreas and regional lymph nodes
3	Distant metastasis-liver, or local metastasis to duodenum, mesentery and/or omentum

Treatment

Surgical extirpation is the treatment of choice for insulinoma after exploratory laparotomy to confirm the diagnosis. This also allows examination of the liver and abdominal contents for metastases. A recent report describing the use of an intravenous methylene blue infusion method for intraoperative identification of primary and metastatic insulinoma in the dog, appears to offer a significant diagnostic advantage with minimal side effects. The information obtained can be used to stage the tumor to provide additional prognostic information. Partial pancreatectomy is the surgical procedure of choice and offers a chance for curing animals with benign adenomas or carcinomas that have not metastasized. Even in dogs with obvious malignant, metastatic or nonresectable tumors, resection of most of the neoplasm may reduce the severity of clinical signs and improve the success of medical therapy. Surgery alone is seldom curative, since most of these tumors have metastasized by the time the patient is presented for examination. Medical management during the postoperative period may be required to control neurologic signs, prevent hypoglycemia, avoid surgically induced pancreatitis and manage postoperative diabetes mellitus.

Dietary management is perhaps the best and most effective way to deal with hypoglycemia, since it is also the most likely method to achieve consistent owner compliance. Frequent feeding (3-6 small meals daily) of foods high in protein, fat and complex carbohydrates provides a relatively stable supply of glucose and prevents the exaggerated insulin secretion associated with large meals.

Medical therapy of hyperinsulinism is usually only palliative but may cause temporary amelioration of clinical signs, thus improving the patient's quality of life. Several drugs have been employed for the hyperglycemic effects. Glucocorticoids are often employed as the first therapy to support blood glucose in hypoglycemic patients. These agents increase blood glucose by inducing hepatic gluconeogenesis and decreasing the peripheral tissue utilization of glucose. They have met with variable success in alleviating hypoglycemia in dogs with insulinoma; their effectiveness varies from weeks up to two years.

Diazoxide, a drug chemically related to thiazide diuretics, has been employed for its hyperglycemic effects in patients with insulinoma. Its hyperglycemic effect can be potentiated by hydrochlorothiazide. Diazoxide directly inhibits pancreatic insulin secretion and glucose uptake by tissues, enhances epinephrine-induced glycogenolysis, and increases the rate of mobilization of free fatty acids. The drug raises blood glucose concentrations in dogs with hyperinsulinism, though reports of its use are infrequent. Anorexia, vomiting and edema are the most common side effects.

Other drugs that have been evaluated in human patients for their hyperglycemic effects include phenytoin, propranolol, L-asparaginase, glucagon, somatostatin and mithramycin. The efficacy and therapeutic protocols for these drugs have not been evaluated in dogs.

Antitumor chemotherapy is usually reserved for patients that do not respond to surgical and other medical management. Streptozotocin, an experimental broad-spectrum antibiotic and antitumor agent, has been used successfully to treat people with insulinoma. Its use was unsuccessful in 2 dogs because of drug-related nephrotoxicosis. Additional drugs used in treatment of insulinoma in people include fluorouracil, doxorubicin, chlorozotocin, alloxan and pentamide. These agents have not been subjected to thorough clinical evaluations in dogs.

Though dogs with insulinoma warrant a poor to grave prognosis due to the aggressive, malignant nature of the neoplasm, owners should be encouraged to attempt treatment with dietary management, medical management and/or surgery. Clinical signs can be ameliorated and improvement in the patient's quality of life can often be maintained for months or, rarely, years.

ADRENAL GLAND

Primary neoplasms of the adrenal cortex can be functional or nonfunctional; however, most appear to be functional resulting in excess glucocorticoid production. Adrenocortical adenomas and carcinomas account for approximately 20% of cases of spontaneous canine Cushing's disease.

Clinical Signs and Diagnosis

There appears to be no sex predilection in canine Cushing's disease, although one report showed that adrenocortical tumors are more likely to occur in female dogs. Poodles, Terriers, Dachshunds, and Boxers appear to be at risk for adrenal neoplasms. The age at presentation has been reported to range from 4 to 14 years.

The clinical signs of hyperadrenocorticism due to adrenal neoplasms are usually identical to those caused by bilateral adrenocortical hyperplasia, and no method is consistently reliable for differentiating between them. Common clinical signs include polyuria, polydipsia, polyphagia, skin atrophy, abdominal enlargement, and hepatomegaly. Other signs include bilateral symmetric alopecia, lethargy, obesity, calcinosis cutis, decreased exercise tolerance, and muscle weakness.

Abnormal laboratory findings are similar to those described for other causes of canine Cushing's disease. Hypokalemia has been reported in several dogs with proven adenoma or carcinoma of the adrenal cortex.

Radiographic evaluation may show enlargement or calcification of the adrenal gland or a mass resembling the adrenal. Special studies or alternate imaging modalities may be required to accurately diagnose adrenal tumors. These include selective adrenal vein angiography, gamma camera imaging after adrenal uptake of ^{131}I -29-iodocholesterol and computer-assisted tomography.

The use of dexamethasone suppression tests may help confirm the diagnosis and differentiate between adrenal tumors and pituitary-dependent Cushing's disease. Dexamethasone, at any dosage, should not suppress elevated plasma cortisol concentrations due to functional adrenal tumors. However, since as many as 30% of pituitary-dependent patients may fail to suppress, a lack of suppression is inconclusive. A higher dose (2.0 mg dexamethasone per kg given intravenously) may disclose suppression and differentiate the cause of the hyperadrenocorticism. The measurement of endogenous plasma ACTH may also help differentiate between pituitary-dependent and adrenal tumor-caused Cushing's disease. The response of the plasma cortisol concentration to exogenous ACTH in dogs with functional adrenal neoplasms is variable. They may show either a normal response or an

abnormally low or exaggerated response to exogenous ACTH. Therefore the ACTH stimulation test is not recommended for routine evaluation of canine Cushing's disease.

Treatment and Prognosis

Adrenalectomy is the treatment of choice for adrenal tumors. It is important to remember that the opposite adrenal gland may be atrophied owing to suppression of pituitary ACTH by the adrenal tumor. Unfortunately, however, the neoplasms are rarely completely resectable at the time of initial surgery. The surgery is difficult and postoperative care may require treatment for hypoadrenocorticism before the opposite adrenal regains normal function.

Medical management using the cytotoxic chemotherapeutic agent o,p'-DDD is not a primary mode of therapy since adrenocortical tumors respond poorly to the drug. It can be attempted if the adrenal carcinoma is metastatic at the time of diagnosis or if the owner refuses surgery. Enzyme blockers such as trilostane and metyrapone have yet to be tried in animals, while ketoconazole has been successful in preliminary studies.

With adrenal carcinoma, metastasis within the adrenal gland, draining lymph vessels, regional lymph nodes, liver, and direct invasion of the caudal vena cava has been observed. Metastasis warrants a poor prognosis. When no metastasis is observed and the tumor is resectable, the prognosis is good.

PARATHYROID GLAND

Neoplasms of the parathyroid glands, usually reflected as clinical disturbances of calcium-phosphorus metabolism, are uncommon in the dog. Primary hyperparathyroidism is the result of overproduction of parathyroid

hormone (PTH) by the parathyroid glands, usually due to the presence of a functional adenoma composed of chief cells. Chief cell carcinomas are rare causes of primary hyperparathyroidism in the dog. The normal control of PTH secretion by the concentration of serum calcium is lost. Hormone secretion is truly autonomous, and the parathyroid gland produces excessive amounts of hormone in spite of hypercalcemia.

Clinical Signs and Diagnosis

Diagnosis of primary hyperparathyroidism is usually difficult, often resulting from the differential exclusion of the other causes of hypercalcemia. Clinical signs include anorexia, emesis, constipation, generalized muscular weakness, polyuria, polydipsia, weight loss and lameness. Radiographic evaluation often reveals severe, generalized skeletal demineralization and, in advanced cases, fractures. Laboratory findings usually include hypercalcemia, normo- or hypophosphatemia, increased alkaline phosphatase, azotemia, and hyposthenuria. Renal function is often normal, or only minimally affected, early in the course of the disease. Parathyroid hormone concentration is usually moderately increased in affected animals, at least until the associated hypercalcemic nephropathy becomes pronounced.

Staging

Parathyroid neoplasms can be clinically staged according to the TMN classification used for head and neck tumors, although this probably offers no advantage clinically since the majority of the tumors are benign functional adenomas.

Treatment and Prognosis

Initial medical management aimed at reducing the adverse effects of hypercalcemia may be necessary before establishing a definitive diagnosis and exploratory cervical surgery. The most important considerations are to correct any pre-existing dehydration and maintain normal hydration while enhancing renal excretion of calcium. Several therapeutic modalities directed toward lowering serum calcium have been widely used in veterinary medicine.

Surgical exploration of the cervical region is both a diagnostic and therapeutic procedure. The goal is to identify all four parathyroid glands and to remove any abnormal tissue. Identification may be enhanced by the use of intravenous methylene blue infusion for intraoperative identification of the parathyroid glands. Subtotal parathyroidectomy is the procedure of choice. In the rare event that a parathyroid gland carcinoma is found to be the cause of the hypercalcemia, invasion of adjacent tissue and metastases to regional lymph nodes can be anticipated. Removal of a functioning adenoma or carcinoma results in a rapid decline in PTH concentrations, if renal and hepatic function are normal. Symptomatic hypocalcemia may develop within 24 to 48 hours following parathyroidectomy. Postoperative hypocalcemia may be the result of hypofunction of the remaining atrophied parathyroid tissue or due to surgically induced damage to remaining parathyroid tissue or its vascular supply. Medical management of postoperative hypocalcemia may require the use of vitamin D therapy and/or, in severe cases, the intravenous administration of calcium-containing solutions. Serum calcium should be monitored daily after surgery until stabilized; then twice weekly for 2 weeks after discharge and then weekly for 1 month. If hypercalcemia persists following surgery, then additional parathyroid lesions, such as functional

metastases or ectopic parathyroid tissue in the mediastinum, must be suspected.

The prognosis for primary hyperparathyroidism is usually guarded to poor since due to chronic hypercalcemic nephropathy or other end-organ damage that is present at the time of diagnosis.

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