WEB CHAPTER 11

Hypercalcemia and Primary Hyperparathyroidism in Dogs

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Differential Diagnosis and Diagnostic Approach to Hypercalcemia

Differential Diagnosis

Hypercalcemia is an abnormality that is usually serendipitously identified on serum biochemical analysis. Disorders associated with hypercalcemia in dogs, in approximate order of incidence at the University of California, include lymphosarcoma, acute and chronic renal failure, primary hyperparathyroidism (PHP), hypoadrenocorticism, vitamin D toxicosis, apocrine gland carcinoma of the anal sac, multiple myeloma, uncommonly in association with a variety of carcinomas (lung, mammary, nasal, pancreas, thymus, thyroid, vaginal, and testicular), and uncommonly in association with certain granulomatous diseases (blastomycosis, histoplasmosis, schistosomiasis). History, physical examination, complete blood count (CBC), urinalysis, serum biochemistry analysis, thoracic and abdominal radiographs, abdominal ultrasound, and examination of cytology and biopsy specimens usually provide adequate information to establish a diagnosis in dogs.

History and Physical Examination

Since hypercalcemia is almost always unsuspected, it is not a mistake to obtain a second blood sample to rule out laboratory error, although in our experience laboratory error is extremely rare. Once hypercalcemia is identified, the veterinarian should review the signalment and history with the owner to identify any clues to a definitive diagnosis that may not have been noted initially. From the history, one can attempt to identify a tentative explanation for the hypercalcemia, such as possible exposure to toxins containing vitamin D (e.g., rodenticides, inappropriate supplementation of food), evidence of pain due to a lytic bone lesion (multiple myeloma or mammary tumor), difficulty eating due to oral lesions associated with renal failure, or a waxing/waning course of illness sometimes noted with hypoadrenocorticism.

The physical examination should also be repeated in an attempt to identify a tentative explanation for hypercalcemia. The spine, ribs, and long bones should be palpated to identify bone pain due to a lytic lesion, while the mammary chain should be evaluated for neoplasia, the oral cavity for "rubber jaw" or lesions consistent with renal failure, the rectal and perineal area for apocrine gland carcinoma of the anal sac or other tumor, the heart rate (slow) and pulse quality (poor) for abnormalities consistent with hypoadrenocorticism, and the peripheral lymph nodes for enlargement suggestive of lymphoma (most dogs with hypercalcemic lymphoma have a mediastinal mass and unremarkable peripheral nodes). Dogs with PHP commonly have a physical examination that does not contribute to a diagnosis (parathyroid masses are almost never palpable).

Routine "Database"

A thorough review of the CBC, serum biochemistry profile, and urinalysis should be completed. The urine specific gravity is commonly less than 1.020 in hypercalcemic dogs with renal disease, hypoadrenocorticism, and PHP. Urinary tract infection is common in these disorders. The CBC may demonstrate a normocytic, normochromic, nonregenerative anemia, which is relatively common in renal failure; hypoadrenocorticism; and various neoplasias. The serum biochemistry profile should also be reviewed to assess the blood urea nitrogen (BUN), creatinine, and serum phosphate for increases consistent with renal failure or vitamin D toxicosis; hyperkalemia and hyponatremia suggestive of hypoadrenocorticism; hyperglobulinemia consistent with myeloma; and hypophosphatemia consistent with PHP. To this point, the only "new" expense would be the repeated serum calcium concentration (if obtained), since the recommendation is to talk with the owner, repeat a physical examination, and review the laboratory results that were already obtained in order to identify the hypercalcemia in the first place.

Radiographs and Ultrasonography

Assuming the review of the history, physical examination, and database has not defined the cause for hypercalcemia, thoracic radiographs are an important next step. The primary purpose for this study is to assess the cranial mediastinum for a mass consistent with lymphoma. If present, fine-needle aspiration or tissue obtained via biopsy should be evaluated. Radiographs also provide an opportunity to evaluate the perihilar area and lungs for neoplasia or systemic mycoses, the spine and ribs for lytic lesions caused by neoplasia, and the heart for microcardia of hypoadrenocorticism. Abdominal radiographs can also be assessed, although ultrasound examination of the abdomen is preferred. The size and consistency of the liver, spleen,

and mesenteric and sublumbar lymph nodes can be evaluated for abnormalities suggestive of malignancy (lymphoma) or other conditions. Diagnostic imaging to evaluate for malignancy (lymphoma) applies to a variety of tumors located in other organs, but tumors other than lymphoma are less common causes of hypercalcemia. When possible, abnormal areas should be aspirated or biopsied to determine the presence or absence of neoplasia. The size and consistency of the kidneys can be assessed, although renal failure should have been ruled in or out on the initial blood test results. The kidneys, ureters, bladder, and urethra should be evaluated for the presence of calculi, which develop in about 30% of dogs with PHP and could develop in any hypercalcemic dog. If these assessments fail to confirm or suggest a diagnosis other than PHP, suspicion for PHP increases. Until a specific cause for hypercalcemia is confirmed, however, lymphoma should never be ruled out. Cervical ultrasonography (discussed in a later section) has become an extremely valuable screening test in dogs with hypercalcemia.

Signalment, History, and Physical Examination in Dogs with Primary Hyperparathyroidism

Dogs with PHP are usually 6 years of age or older. The mean age from our series of 335 dogs with PHP was 10.7 years. Dogs of both genders are almost equally affected, about 14% of affected dogs are Keeshonds, but a huge number of breeds have been represented. The mean body weight of the 335 dogs was 24 kg.

Dogs with PHP, unlike those afflicted with most other diseases that cause hypercalcemia, are usually not ill or not as ill. Owners of 124 of 335 PHP dogs (37%) had observed no hypercalcemia-related abnormalities in their pet. Blood had been obtained from these dogs usually for a routine geriatric evaluation, as part of a preanesthesia screen prior to a dental procedure, or for an unrelated condition.

The most common owner-observed abnormalities in dogs with PHP were polyuria and polydipsia (57% of dogs), lethargy/weakness/decreased activity (43%), decreased appetite (30%), weight loss or muscle wasting (10%), shivering or trembling (7%), and vomiting (5%). However, even when clinical signs are observed, they are often relatively mild. When signs were observed, they had been present for as little as a few days to more than 2 years. Only about 5% of the PHP dogs with urolithiasis or urinary tract infection had appropriate clinical signs (i.e., straining to urinate, increased frequency of urination, and hematuria). Since more than 90% of the dogs identified as having both PHP and cystic calculi were asymptomatic for their stones, the indication for abdominal imaging in any hypercalcemic dog is emphasized.

In 254 of 335 dogs with PHP (76%), the medical record stated that no abnormalities relative to the diagnosis of PHP were noted on physical examination. When noted, abnormalities included muscle wasting, the dog being slow to rise, and obesity in some dogs and thin body condition in others. Each of these problems was seen in fewer than 10% of dogs with PHP.

Clinicopathologic Abnormalities in Dogs with Primary Hyperparathyroidism

Hypercalcemia (i.e., serum total calcium concentrations >12 mg/dl; reference range of 9.9 to 11.6 mg/dl) was identified in all 335 dogs with PHP in our series. This "sensitivity" (100%) may be misleading since we do not evaluate dogs for hypercalcemia unless this criterion is met. The mean serum total calcium concentration was 14.4 mg/dl, with a range of 12.1 to 24.2 mg/dl. About 50% of dogs with PHP had serum total calcium concentrations higher than 12 and below 14 mg/dl; about 33% had values higher than 14 and below 16 mg/dl; about 10% had values higher than 16 and below 18 mg/dl; and slightly more than 5% had values higher than 18 mg/dl. The mean plasma ionized calcium concentration in the 335 dogs with PHP was 1.77 mmol/L (range 1.22 to 2.58; normal reference range 1.12 to 1.41 mmol/L). Just under 4% of the dogs with PHP had a serum ionized calcium concentration within the reference range, almost 33% had values between 1.42 and 1.65 mmol/L, and almost 50% had concentrations between 1.66 and 1.90 mmol/L, with the remaining having concentrations higher than 1.91 mmol/L.

A common reason for *referral* of dogs ultimately diagnosed with PHP is the referring veterinarian's concern that if not treated, hypercalcemia would place dogs at risk for developing renal failure. However, this is not the case. The mean BUN concentration in 335 dogs with PHP (~18 mg/dl) was at the low end of the reference range of 18 to 28 mg/dl, the mean serum creatinine concentration (0.9 mg/dl) was well within the reference range (0.5 to 1.6 mg/dl), and the mean serum phosphate concentration (2.7 mg/dl) was less than the reference range (3.0 to 6.5 mg/dl). All these values were significantly less than values from 200 dogs of similar ages that were randomly reviewed from our hospital population. In other words, dogs with PHP seem protected from renal failure rather than predisposed to this condition. Duration of hypercalcemia was also not a factor, since some dogs with PHP went years without treatment. Owner-observed polyuria and polydipsia were well supported by finding a mean urine specific gravity of 1.012 in 335 dogs with PHP. About 30% of these dogs had urinary tract infections and about 30% had cystic calculi; some had both. Although renal failure is rare and not a reason for treating a dog that has PHP, infection and calculi are common and certainly should be among the reasons for recommending therapy.

Confirmation of Primary Hyperparathyroidism (Use of Serum Parathyroid Hormone and Parathyroid Hormone–Related Protein Concentrations)

Are Parathyroid Hormone Assay Results Vital?

The differential diagnosis for hypercalcemia is relatively short and veterinarians should be able to rule in or out most conditions using the diagnostic approach

recommended earlier in this chapter. Sophisticated and relatively expensive studies, such as assaying serum parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) concentrations, are less important in this context. Serum PTH concentrations have been assessed on a large number of dogs with PHP that we have treated since the early 1980s. However, a majority of these results were available days to weeks *after* treatment had been completed. In other words, diagnosis and treatment were completed without these assay results because employing a logical approach in determining the cause of hypercalcemia was successful. This is not to suggest that the assays have no value, but rather that in many dogs the assay results are not vital.

Serum Parathyroid Hormone Concentrations

Serum PTH concentrations are commercially available, and normal-to-increased concentrations confirm the diagnosis of PHP in non–renal failure hypercalcemic dogs. Dogs with renal failure may also have increased serum PTH concentrations; however, within the context of the renal parameters, the serum phosphate concentration, ionized serum calcium concentration, and other pertinent information, dogs with PHP can usually be readily distinguished from those with renal failure. As serum calcium concentrations rise in healthy dogs, serum PTH concentrations should become undetectable. Therefore the term *normal range* can be misleading, since the average dog with PHP has a serum PTH concentration that is "normal." This seems counterintuitive, whereas the term *reference range* provides better understanding of the condition. Increasing serum calcium concentrations should decrease serum PTH concentration below the reference range while values within the reference range would be physiologically abnormal. Using a reference range for serum PTH concentrations of 2 to 13 pmol/L, 198 of 335 dogs with PHP (~60%) had serum PTH concentrations within that range; 36% had results of 2.3 to 7.9 pmol/L, 24% had results of 8.0 to 13.0 pmol/L, 16% had results between 13 and 20 pmol/L, and 24% had results higher than 20 pmol/L.

Serum Parathyroid Hormone–Related Protein Concentrations

Increased serum PTHrP concentrations in hypercalcemic dogs would be most consistent with lymphoma or apocrine gland carcinoma of the anal sac. If a specific explanation for hypercalcemia remains elusive, but malignancy remains possible, "response to treatment" should be a *last resort*. Before any medication is given, aspiration or biopsy of lymph nodes, spleen, and/or liver should be considered in an attempt to establish a diagnosis of malignancy, including lymphoma. Lymphoma is emphasized because it is a common condition; occasionally it can be a difficult diagnosis to confirm, especially after glucocorticoids have been administered.

Localizing Parathyroid Tissue Causing Hyperparathyroidism

Cervical Ultrasound

Ultrasound examination of the cervical area is generally available, noninvasive, and relatively cost efficient. However, ultrasound value, as much as any diagnostic tool used in veterinary medicine, is operator dependent. The skill of the individual performing the examination is a major factor in assessing the value of this diagnostic aid. Parathyroid tumors are typically round-to-oval hypoechoic masses that measure 4 to 8 mm in greatest length and are closely associated with a thyroid lobe; some are as large as 20 mm in greatest diameter. Most masses are 4 to 6 mm in greatest diameter. Cervical ultrasound was performed in 255 of the dogs with PHP in our series. In 221 of these dogs, a solitary parathyroid mass was visualized. In 218 of these 221 dogs, the diagnosis was correct. In 15 of these 221 dogs, the diagnosis of a solitary parathyroid mass and a single (or multiple) thyroid mass was correct. At the time of diagnosis, one dog had two parathyroid masses identified and removed at surgery, although only one mass had been reported on the ultrasound examination. In each of two dogs, ultrasound diagnosis reported both solitary thyroid and parathyroid masses; this was later discovered to be two parathyroid adenomas. About 5% of the dogs with PHP in our series had thyroid cysts, adenomas, or carcinomas at the time of PHP diagnosis.

Ultrasound examination suggested that each of 12 dogs had two parathyroid masses; this was actually true for nine of the dogs. One dog had only one parathyroid mass and two dogs each had a solitary parathyroid and a solitary thyroid mass. Ultrasound examination failed to identify a parathyroid mass in five dogs, each of which had a solitary parathyroid tumor removed at surgery. Each of 31 dogs (9% of the 335) had two parathyroid masses correctly identified via ultrasonography at the time that PHP was diagnosed.

Cervical ultrasonography has become a routine component of evaluating hypercalcemic dogs. Failure to identify at least one enlarged parathyroid gland in a dog suspected of having PHP would not eliminate that diagnosis. However, failure to visualize a mass is reason to reconsider the diagnosis.

Other Tests

Abnormal parathyroid tissue has been localized in humans by using technetium 99 (Tc^{99}) sestamibi nuclear scintigraphy. Results in dogs with PHP have been inconsistent at best and the procedure is not recommended. Recent attempts to localize abnormal parathyroid tissue using selective venous sampling to measure the serum concentrations of PTH were not satisfactory.

Treatment of Primary Hyperparathyroidism

Pretreatment Considerations: Candidates for Percutaneous Versus Surgical Treatment

Treatment options for PHP include surgical removal and percutaneous heat or ethanol ablation. Several

factors should be considered prior to suggesting a treatment recommendation. If a male dog has cystic or urethral calculi, surgery or retrograde urohydropulsion is recommended to remove all calculi. The decision to perform surgery on dogs with renal or ureteral calculi must be considered on an individual basis. Dogs with evidence of both a parathyroid mass and a thyroid mass should probably undergo surgery. Dogs undergoing surgery for calculi in the urinary tract should have their parathyroid mass removed during the same anesthesia.

Candidates for ultrasound-guided ablation treatment must not have a mass too closely associated with one of the carotid arteries nor can the mass be too small to confidently have a needle placed percutaneously. Masses larger than 12 to 15 mm in greatest diameter are not common and are often managed surgically. For dogs with two contralateral parathyroid masses, surgery is recommended or the percutaneous treatment should be "staged" at least 30 days apart to avoid any possibility of iatrogenic laryngeal paralysis, an uncommon but possible problem.

Pretreatment Considerations: Serum Calcium Concentrations

Dogs are not at risk for developing hypocalcemia in the first 48 hours after surgical or percutaneous therapy, regardless of the pretreatment serum calcium concentration or duration of PHP. If the pretreatment serum calcium concentration is between 12 and 14 mg/dl, vitamin D therapy is usually withheld. In these dogs, serum calcium or ionized calcium concentrations are monitored once or twice daily for 5 to 7 days after treatment. Vitamin D therapy is only instituted if the serum calcium concentration decreases below 9 mg/dl, the ionized calcium decreases below 0.95 mmol/L, or clinical signs of tetany are observed. Observation of any such response, while relatively uncommon, usually takes 3 to 7 days.

If the serum calcium concentration prior to therapy is 15 mg/dl or higher or if a dog has more than one parathyroid mass, the incidence of postsurgical hypocalcemia is greater. In these patients, vitamin D therapy is usually initiated the morning of the treatment (calcitriol, 10 to 15 ng/kg q12h for first 3 to 4 days and then 2.5 to 5 ng/kg q12h). The decision regarding vitamin D therapy in dogs with a pretreatment calcium of 14 to 15 mg/dl is open. Whenever vitamin D therapy is used, monitoring of serum calcium is carried forth as described and parenteral calcium is only administered if tetany occurs or is thought to be imminent. Vitamin D is then tapered to ever-decreasing dosages over a 2- to 6-month period. Once the serum calcium concentrations plateau at a safe concentration (usually >9.5 mg/dl), the dog should be returned to the owner. Serum calcium concentrations can be checked frequently initially and then usually every 2 weeks to support any scheduled dose reduction. Dose reduction is usually by 50% every 2 weeks.

Percutaneous Ultrasound-Guided Heat Ablation

Approximately 55% of the dogs we diagnose as having PHP have surgery and about 45% undergo percutaneous ultrasound-guided ablation. Both procedures have been used with excellent results. Dogs that meet the inclusion criteria for percutaneous therapy are placed under anesthesia and, with ultrasound guidance, have an insulated needle placed into the parathyroid mass. The needle is attached to a radiofrequency unit (radiofrequency waves are naturally converted to heat at the needle tip). The wattage is started at a low level and increased based on observing a "bubbling" appearance to the tissue. The needle tip is repositioned several times to ensure, as much as possible, that the entire parathyroid mass has been ablated. Percutaneous ultrasound-guided heat ablation requires 15 to 30 minutes of anesthesia and is usually less expensive. Post–heat ablation management of the dog is identical to the management following surgical removal of a parathyroid mass.

Percutaneous Ultrasound-Guided Ethanol Ablation

Percutaneous ultrasound-guided ethanol ablation is no longer recommended. The procedure used resembled that for percutaneous ultrasound-guided heat ablation except the needle was connected to a syringe containing a volume of ethanol similar to the calculated volume of the parathyroid nodule. Ethanol was infused slowly in an effort to expose it to all tissue, with the needle tip repositioned several times to aid in accomplishing this goal. Unfortunately, leakage of this caustic material invariably occurred following the procedure. Such leakage could cause nerve damage and secondary laryngeal paralysis.

Surgery

Complete exploratory surgery of both thyroid lobe areas, with both ventral and dorsal surfaces of the thyroid lobes examined, is recommended for dogs with PHP. In most of these dogs, the abnormal parathyroid tissue is solitary, off-color, and larger than normal parathyroid tissue, easily recognized and easily extirpated. Only abnormal parathyroid tissue is removed if possible, although when a parathyroid tumor lies within a thyroid lobe, that thyroid lobe is usually removed. If no parathyroid mass is observed and the diagnosis is thought to be correct, one thyroid/parathyroid complex should be removed and examined histologically. If two abnormal parathyroids are observed, both should be removed.

Posttreatment Care

Dogs are kept in-hospital for 5 to 7 days after treatment to monitor serum calcium concentrations and, more importantly, to keep the dog quiet. Since most dogs are quiet in-hospital, the quiet hypocalcemic dog is less prone to clinical tetany than would be the case if the dog is active. Dogs that are unusually active in-hospital are

sent home. We usually monitor serum total calcium concentrations twice daily until release from the hospital.

Histology

Parathyroid tumors have been histologically classified as adenoma, hyperplasia, or carcinoma. These classifications have not had use clinically, since all parathyroid masses act biologically similar. We have not experienced a dog with local tumor invasion nor with distant metastasis. Recurrence rate is about 10% regardless of the histology.

References and Suggested Reading

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