Canine Primary Hyperparathyroidism

David S. Mills

Mississippi State University College of Veterinary Medicine

Class of 2019

Clinicopathologic Conference

November 9, 2018

Advisors:

Patty Lathan, VMD, MS, DACVIM

Harry Cridge, MVB

Introduction

Canine primary hyperparathyroidism (PHPT) is an endocrine disease that results from a change to one or more of the parathyroid glands that causes an autonomous secretion of parathyroid hormone by the chief cells. The most common cause is a benign functional parathyroid adenoma that is seen in 90% of cases (3). Malignant tumors of the parathyroid glands are uncommon and usually non-invasive (2). PHPT leads to hypercalcemia which can have deleterious effects on any tissue in the body but often there are no clinical signs. Diagnosis may take time but is often straightforward if it is performed appropriately. There are multiple treatment options available. Successful treatment must include appropriate post-operative monitoring of calcium status, regardless of the therapeutic option selected (2,6,3).

History and Presentation:

Diamond Ringo, a 9-year-old neutered male Maltese, presented to his primary veterinarian on May 9, 2018 for his annual examination and vaccines. During this appointment the owners reported that Diamond seemed reluctant to jump on furniture, and the primary veterinarian performed bloodwork. The bloodwork revealed an increased total calcium level at 15.2mg/dL (Reference range: 8.4 – 11.8mg/dL). Other findings include: a low-normal phosphorus of 2.9 mg/dL (Reference range: 2.5-6.1mg/dL), a BUN of 24 mg/dL (Reference range: 9-31 mg/dL), a creatinine of 0.9 (Reference range: 0.5-1.5mg/dL), and an SDMA of 13 ug/dL (Reference range: 0-14 ug/dL). The owner agreed to return to the primary veterinarian for a recheck of calcium level, before pursuing further diagnostics. Upon returning, for examination, the patient’s calcium concentration was still elevated. Radiographs were taken which revealed four bladder stones. A urinalysis was performed which revealed no significant findings. The primary veterinarian then

performed a complete ACTH stimulation test, which ruled out hypoadrenocorticism. A malignancy panel was submitted to Michigan State University, and Diamond was hospitalized on fluids and pain medications while awaiting the results. His calcium levels remained elevated for five days while he was hospitalized. On 5/17/18, the results of his malignancy panel revealed a PTH of 4.40 pmol/L (Reference range: 0.5-5.8 pmol/L), an ionized calcium level of 1.98 mmol/L (Reference range: 1.25 – 1.45 mmol/L), and PTHrP was 0. These results are consistent with a diagnosis of primary hyperparathyroidism. Diamond Ringo was then referred to the MSU-CVM Internal Medicine Service.

Anatomy and Pathophysiology:

Calcium is the most abundant mineral in the body. 99% of all calcium is stored in bones and teeth, and only 1% is in the soft tissue and blood. Of that 1%, only one-tenth of it is in the plasma at any given time. 30-40% of plasma calcium is protein-bound, and 10% is complexed with anions such as lactate, citrate, bicarbonate and phosphate. The remaining 50-60% is ionized calcium, which is the biologically active form of calcium (3,8). An acidic pH within blood leads to an increase in ionized calcium levels in contrast to an alkalotic blood pH, which leads to less ionized calcium (3). Calcium is critical for many biological functions such as muscle contraction including heart, blood coagulation, enzyme activity, neuronal excitability, hormone release, membrane permeability and more. The three primary hormones that control calcium homeostasis are parathyroid hormone (PTH), calcitriol, and calcitonin. (2,7).

Most dogs have four parathyroid glands. There can be rare ectopic glands due to developmental abnormalities such as close proximity of the developing thymus causing portions to break off and migrate with the thymus and develop in abnormal locations. Normally, the glands are located external to the thyroid capsule (external parathyroid gland) or inside the

thyroid capsule (internal parathyroid gland). These parathyroid glands are small and measure 2-4mm in diameter.

Parathyroid hormone (PTH) is produced by the chief cells of the parathyroid gland which contain calcium-sensing receptors to regulate synthesis and release of PTH. It is primarily regulated by a negative feedback mechanism involving serum calcium levels. In normal animals, calcium and PTH have an inverse linear relationship (2). The main role of PTH is to maintain adequate calcium levels in the blood and to regulate phosphorous levels through mechanisms involving the bones, kidneys and intestines (2,3,7). PTH stimulates release of calcium and phosphorous from bone. PTH works directly on the kidneys to enhance calcium reabsorption while promoting phosphorous excretion. Under the influence of PTH, the kidney has a more dominant effect on phosphorous levels than bone resulting in an overall change of increased calcium and decreased phosphorous. PTH also indirectly works on the gastrointestinal system by causing an increase in the synthesis of the active form of vitamin D3 (calcitriol), via increasing the activity of 1α-hydroxylase (3,7,2,4).

Vitamin D3 is found in the diet and plays a vital role in calcium homeostasis. Cholecalciferol is the inactive form of vitamin D3. Once ingested it is transported to the liver via the portal circulation and intestinal lymphatics. After cholecalciferol is transported to the liver, it is hydroxylated by 25 hydroxylase to form 25(OH)D (aka calcidiol) which binds vitamin D binding protein in circulation. 25(OH)D is then hydroxylated via 1α hydroxylase to 1,25 (OH) D aka calcitriol. Calcitriol is the most active naturally occurring vitamin D metabolite. This synthesis is expedited in response to an increase of PTH or a decrease of serum phosphorous. Calcitriol causes a decrease in PTH. Calcitriol also works on the small intestines and kidneys to increase calcium and phosphorous absorption. In large quantities, it stimulates bone resorption

increasing calcium and phosphorous levels. It is also vital for PTH to cause bone resorption. (3,7,2).

Calcitonin is the last major player in calcium homeostasis. It is secreted by parafollicular cells (C cells) of the thyroid gland. Calcitonin has the opposite effect as the other two hormones and is triggered by increased levels of calcium. Calcitonin has an overall lesser effect on circulating calcium levels. This is proven because complete removal of the thyroid gland often has very minimal effects on serum calcium levels (3,7,2).

Hypercalcemia can have toxic effects on any body tissue but most importantly the kidneys, nervous system, musculoskeletal and cardiovascular system. The clinical signs vary depending on the severity, chronicity, and causative underlying disease. At drastically elevated levels, higher than 18 mg/dl, clinical signs are extremely severe and can be life threatening (6). The most common clinical signs observed are lethargy or anorexia, polyuria and polydipsia, vomiting, constipation, muscle weakness, depression, and tremors. There are often no clinical signs seen, which can make it difficult to detect (3).

The most common cause of hypercalcemia in dogs is various forms of neoplasia(3). The most common mechanism of these neoplasms is humoral hypercalcemia of malignancy mediated by PTHrP or parathyroid hormone-related peptide. (8,2,7). Other causes in dogs include renal failure, primary hyperparathyroidism, and hypoadrenocorticism in descending frequency (3).

Primary hyperparathyroidism (PHPT) can occur via neoplastic (adenoma or carcinoma) or hyperplastic changes. Hyperplastic changes are rare and often involve more than one parathyroid gland. Most commonly, it is a single benign functional adenoma that accounts for 90% of all cases, while carcinomas account for 5% of these cases. PHPT accounts for around

10% of hypercalcemia cases seen in canines. PHPT causes an autonomous secretion of parathyroid hormone that is not controlled by negative feedback. There is no sex predilection, but it commonly occurs in older animals with a mean age of 11 years old (2,3). A study showed that Keeshondens are the most commonly affected breed due to an autosomal-dominant, single gene mutation inheritance. Genetic testing has shown a high association with PHPT in this breed. There is a single report of a familial form of neonatal hyperparathyroidism in a litter of German Shepherd puppies; it was suspected that it was an autosomal-recessive form of inheritance (4).

42% of PHPT cases have no clinical signs associated with hypercalcemia (3,4,2). The most common clinical signs seen with primary hyperparathyroidism include polyuria and polydipsia, weakness, decreased activity, decreased appetite, weight loss, and vomiting. Lower urinary tract signs, such as pollakiuria, stranguria, and hematuria, are commonly seen due to urolithiasis and urinary tract infection. Other less common signs can include anemia, ECG changes, hypertension, depression, pancreatitis, skeletal demineralization and pathologic fractures, lameness, stiff gait, kidney stones, psychosis, somnolence, muscle atrophy, seizures and soft tissue calcification. If the calcium-phosphorous ratio exceeds 70, it can result in calcification of soft tissues which may result in organ damage. However, this is rare in primary hyperparathyroidism (3,9,4,7,2). Multiple studies have evaluated the incidence of renal failure in cases of primary hyperparathyroidism. A north American study revealed that PHPT was an uncommon cause of renal failure. However; one study from Great Britain revealed that renal failure developed in 7 of 29 PHPT dogs. However, this may be attributed to a smaller sample size or that the dogs in the North American study were diagnosed and treated earlier (4). It is even speculated that PHPT in dogs may be renal protective (2).

Diagnostic Approach:

The diagnosis to PHPT is relatively easy when performed appropriately. The primary diagnostic approach is to first rule out other differentials, starting with neoplasia which is the most common diagnosis (2,3). A thorough history, physical exam, and diagnostic work up must be performed to rule out other causes of hypercalcemia which include hyperparathyroidism, hypoadrenocorticism, renal disease, vitamin D toxicosis (including granulomatous disease, plants, and rodenticides), idiopathic, iatrogenic, osteolytic, neoplastic, and spurious (2,3). Young growing animals can have calcium levels above the reference interval. The history should include questions about appetite, activity, drinking, urination as well as diet, supplements, and whether there is access to rat bait or any toxic plants (4,6).

A complete blood count, chemistry panel, and urinalysis should be performed to evaluate the underlying cause of hypercalcemia. Focus should be placed on alterations in renal values and electrolytes, such as sodium, potassium and phosphorous (2,3). If phosphorous is low or within the lower half of the reference range, primary differentials should include humoral hypercalcemia of malignancy or PHPT. If serum phosphorous is increased with normal renal function, then the primary differentials should include hypervitaminosis D or osteolysis due to bone neoplasia. Kidney failure can cause hypercalcemia, but hypercalcemia can also cause kidney failure, especially in cases with high phosphorous concentrations. Ionized calcium levels tend to be normal or decreased in kidney failure patients. Other signs that can indicate renal insufficiency include nonregenerative anemia, proteinuria and small or irregular kidneys (2,4). Once hypercalcemia has been confirmed, the calcium level should always be rechecked using a non-lipemic blood sample from a 12 hour fasted animal to rule out any spurious test results before performing further diagnostics (6).

The next steps in diagnostic testing are directed based on results of the bloodwork and urinalysis. If there is a suspicion of typical or atypical Addison's disease, then an ACTH stimulation test should be performed. If there is decreased or low-normal phosphorous concentrations in an animal showing systemic signs of illness, then it is more likely due to neoplasia than primary hyperparathyroidism (6). Radiographs should be performed next to look for masses, osteolytic lesions, or any other abnormalities such as bladder stones. Bladder stones can be seen in 25% of PHPT cases (2). Ultrasound of the cervical region to look for an enlarged or abnormal parathyroid gland by experienced radiologists can identify parathyroid adenomas in 90% of cases (2,4). Most parathyroid adenomas are between 4 mm and 9 mm in diameter, and they are easily distinguishable from normal parathyroid glands (2). Another options includes a malignancy panel which measures serum ionized calcium, PTH levels, and PTHrP. This is most beneficial when trying to differentiate between primary hyperparathyroidism and neoplasia. Neoplastic conditions may have an elevated PTHrP with decreased or even nondetectable levels of PTH. Both primary hyperparathyroidism cases usually have undetectable PTHrP with normal to increased levels of PTH, whereas both conditions have elevated ionized calcium levels. In 73% of dogs with primary hyperparathyroidism, the PTH levels were within the reference range which is considered abnormal because the persistently elevated calcium levels should result in a decreased PTH level (2,3,4). There are other diagnostic tools available, but they are not routinely recommended or performed. These tests include nuclear scintigraphy, calcitriol measurements, selective venous sampling of PTH, and new methylene blue infusions (2).

Case Management:

Upon presentation at MSU-CVM on 6/7/2018, Diamond Ringo was bright, alert and responsive with normal vitals, including ECG and blood pressure. The abnormalities noted by

the primary veterinarian were all appreciated, and a grade V/VI left sided heart murmur was auscultated. Bloodwork was repeated, which revealed an elevated calcium level and a slightly decreased phosphorous. Abdominal radiographs revealed four irregularly-shaped cystoliths, and incidental findings of mild hepatomegaly and smooth periarticular proliferation surrounding the head of the right thirteenth rib. Thoracic radiographs were taken to better evaluate the cardiac silhouette. Radiographs revealed mild left sided heart enlargement with no signs of congestive heart failure. Further cardiac diagnostics were declined by the owner. Ultrasound of his cervical region revealed a tubular, smoothly marginated, hypoechoic structure that measured 0.32 x 0.6 x 0.38cm medial to the right common carotid artery within the region of the right lobe of the thyroid gland. Differentials for this structure include neoplasia, hyperplasia or a thyroid cyst. There was also a pinpoint, ovoid, hypoechoic structure within the left lobe of the thyroid gland but appeared normal otherwise. Diamond was discharged after scheduling an appointment with the MSU-CVM surgery department.

Treatment:

In dogs with primary hyperparathyroidism immediate treatment is often unnecessary (2,4). One treatment option is saline diuresis with 0.9% NaCl, which helps promote excretion of calcium in the urine. Once the patient is adequately hydrated, furosemide can be administered to inhibit calcium reabsorption in the ascending Loop of Henle (3,4). Glucocorticoids can be used to decrease bone resorption and decrease calcium absorption by the gastrointestinal system and kidneys. It is important to come to a definitive diagnosis prior to starting glucocorticoids, as they may inhibit future diagnostics, especially with conditions such as lymphoma. Occasionally, salmon calcitonin is used to quickly lower serum calcium levels, but it is considered a weak and short-lived treatment (2,3). Bisphosphonates work by inhibiting osteoclasts, and pamidronate is

the preferred choice for dogs. Pamidronate can decrease calcium concentrations for multiple weeks (3,2,4). Bicarbonate can also be used to alkalinize the blood and thus decrease the ionized calcium fraction, but this option is very short acting. Calcimimetics are a relatively new drug class used that bind to calcium sensing receptors and inhibit the production of PTH. Less commonly used treatments that may help include mithramycin, EDTA, and dialysis. (2).

Ultimately, the preferred treatment for PHPT is surgical removal of the affected gland(s). Usually only one parathyroid gland has to be removed, but up to three can be safely removed without causing permanent hypoparathyroidism. The prognosis for these cases is excellent, as surgery is considered curative if it is a solitary adenoma. Other treatment options include ethanol ablation and heat ablation. In one study, the success rates were 87% for ethanol ablation, 92% for heat ablation, and 96% for surgery(1). Post operatively, hypocalcemia can occur three to seven days due to atrophy of the unaffected parathyroid glands (2). It is vital to monitor calcium levels post operatively, and many different protocols exist (3). Hypocalcemia requires supplementation with calcitriol with or without calcium carbonate, and calcitriol can be slowly discontinued after a few months. If hypocalcemia becomes severe (iCa < 0.8mmol/L) and clinical signs such as muscle fasciculations, facial pruritus or bradycardia occur, treatment with intravenous calcium gluconate may be required. When giving calcium gluconate the patient should be monitored via ECG for changes such as bradycardia or ventricular premature contractions. There have been studies trying to associate the severity of hypercalcemia before treatment with the probability of hypocalcemia post-treatment. The results are conflicting, and only one study showed moderate correlation. Therefore, clinicians should use clinical signs and frequent calcium monitoring to determine when and if calcium supplementation is needed (5).

Case Outcome:

Diamond Ringo presented to the MSU-CVM surgery service on 6/18/18 and an istat as performed which revealed an elevated ionized calcium (1.65 mmol/L). A cervical exploratory surgery was performed to allow for a right sided parathyroidectomy. The right external parathyroid gland was removed and submitted for histopathology and the biopsy was consistent with an adenoma. Next, a cystotomy was performed, and four bladder stones were removed and submitted for analysis. The stones were composed of calcium oxalate. A section of the bladder wall was submitted for culture and revealed no growth. Diamond's serial post-operative ionized calcium levels were all normal to mildly decreased, so calcium supplementation was not required. He returned to his primary veterinarian on June 27th, for a recheck of calcium levels, and the calcium concentration was within normal limits. According to his owner, Diamond Ringo has been doing very well at home and has had no complications.

References:

1. Rasor, Liberty, et al. “Retrospective Evaluation of Three Treatment Methods for Primary Hyperparathyroidism in Dogs.” Journal of the American Animal Hospital Association, vol. 43, no. 2, 2007, pp. 70–77., doi:10.5326/0430070.
2. Ettinger, Stephen J., and Edward C. Feldman. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat. 7th ed., vol. 2, Elsevier, 2005.
3. Dr. Lathan – Comparative Endocrinology lectures on Calcium and Hypercalcemia
4. Schaefer, Carmen, and Richard Goldstein. “Canine Primary Hyperparathyroidism.” VetFolio, Compendium, Aug. 2009, www.vetfolio.com/internal-medicine/canine-primary-hyperparathyroidism.
5. Dear, J.d., et al. “Association of Hypercalcemia Before Treatment With Hypocalcemia After Treatment in Dogs With Primary Hyperparathyroidism.” Journal of Veterinary Internal Medicine, vol. 31, no. 2, 2017, pp. 349–354., doi:10.1111/jvim.14644.
6. Nelson, Richard W. “Hypercalcemia in Dogs and Cats: Etiology and Diagnostic ...” Veterinary Information Network, School of Veterinary Medicine, University of California, 2002, www.vin.com/apputil/content/defaultadv1.aspx?id=3846169&pid=11147.
7. Hall, John Edward. Pocket Companion to Guyton and Hall Textbook of Medical Physiology. 12th ed., Elsevier, 2016.
8. “Calcium.” EClinpath, Cornell University College of Veterinary Medicine, www.eclinpath.com/chemistry/minerals/calcium.
9. Stoelting, Robert K., and Stephen F. Dierdorf. Anesthesia and Co-Existing Disease. Churchill Livingstone, 2002.