Pacific Tide

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Dr. Garcia received his undergraduate degree from UCLA and his Doctorate in Veterinary Medicine from UC Davis in 2008. After a year long rotating internship at the University of Minnesota he returned to UC Davis, in 2009, to complete an internal medicine residency. He became board certified in internal medicine in 2012. Dr. Garcia has special interests in endoscopy, gastroenterology, urology and fungal infectious diseases. He shares his life with his wife Catherine, two children, a dog, cat and parrot. In his spare time he enjoys backpacking and taking his children to explore tide pools.

Hypercalcemia Diagnosis in Dogs

Hypercalcemia is an uncommon finding on a chemistry panel in dogs. A calcium level on a chemistry panel is representative of total calcium (tCa) in the blood, which actually is composed of three fractions of calcium. Ionized calcium (iCa) makes up ~50% of tCa, and is the biologically active form of calcium. This is the calcium that the body senses and has effects at the cellular level. The other fractions are calcium bound to proteins (mainly albumin) and calcium complexed to anions, which make up ~35% and 15% of calcium respectively.

Calcium is normally very tightly regulated by the parathyroid glands through the actions of parathyroid hormone (PTH). The parathyroids "sense" the amount of iCa in the blood, and PTH is released in response to a low iCa level. PTH has multiple effects in the body, with the net result to increase iCa in the body. This is done through liberating calcium (and phosphorus) from bone, increasing calcium (and phosphorus) absorption from the intestines via vitamin D (which is made active by PTH) and retaining calcium from the urine while excreting extra phosphorus. The excretion of excessive phosphorus is a very important protective mechanism, as calcium and phosphorus tend to complex with each other. If both are present in excessive amounts, dangerous ectopic mineralization can occur, causing mineralization of blood vessels, gastric lining and even fatal renal failure. There is risk of metastatic mineralization whenever the calcium-phosphorus product (tCa x Phos) is greater than 60-80.

Elevated calcium can be found as an incidental finding or in patients that are very clinically ill. Clinical signs commonly seen with hypercalcemia include PU/PD, lethargy, inappetance or even a lack of clinical signs. Less common signs include vomiting, muscle spasms, constipation, lower urinary tract signs (due to calcium-containing stones) and rarely, seizures or cardiac dysrhythmias.

A pneumonic to remember the differentials associated with hypercalcemia is HOGS IN YARD.

- Primary **H**yperparathyroidism
- **O**steolytic/osteoclastic disease
- **G**ranulomatous disease

- **S**purious
- **I**diopathic
- **N**eoplasia
- **Y**outh
- **A**ddison's disease
- **R**enal Failure
- Vitamin **D** toxicity

Primary hyperthyroidism (1°PTH) is an uncommon endocrine disease caused by hyperplastic/adenomatous change to one or more of the parathyroid glands that causes unregulated release of PTH. This results in elevated calcium and often low normal to low phosphorus levels. 1°PTH is seen in older dogs, and is inherited in Keeshonden, where it can be seen at younger ages. Dogs with 1°PTH usually are clinically not sick, which is different from most other causes of hypercalcemia.

Osteolytic/osteoclastic disease is a very rare cause of hypercalcemia, but can be seen with certain types of generalized bony destruction (multiple myelomas etc). They tend to have normal phosphorus levels. These patients will usually be sick with bone pain often appreciated on exam. Focal osteosarcomas do not cause hypercalcemia.

Granulomatous disease is a rare cause of hypercalcemia in dogs. Most causes are infectious diseases. Macrophages in these granulomas create a vitamin-D analog that causes hypercalcemia and generally normal phosphorus levels. These dogs will usually be ill, often with fevers and cough or other signs associated with their underlying disease. This is most recognized in dogs with Blastomycosis, a fungal infection seen in the Midwest and East, but can be seen with other fungal infections, chronic, atypical bacterial infections (Mycobacteria) and even liver flukes. Travel history is going to be very important, as most causes of granulomatous disease are not seen in California.

Spurious, or false elevations in calcium can be seen due to preanalytical (blood draw, blood collection tube issues) or analytical (machine) errors. All hypercalcemias should be confirmed with a second blood draw and submission to an outside lab if initially performed in-house.

Idiopathic (without identified cause) hypercalcemia is only recognized in cats and is not a diagnosis in dogs.

Neoplasia is the overall most common cause of hypercalcemia in dogs. Multiple cancers have been shown to cause hypercalcemia. Lymphoma is the top overall cause of hypercalcemia in dogs (50% in one study), with anal sac adenocarcinomas, a variety of other carcinomas and occasional mesenchymal cell tumors also responsible. Though multiple mechanisms of neoplasia-induced hypercalcemia have been documented, the most common is tumor production of a hormone called Parathyroid Hormone Related Peptide (PTHrP). PTHrP has a structure very similar to PTH, and has similar biological effects. It is not made in adult animals except with neoplasia. Dogs with hypercalcemia of malignancy will generally have normal phosphorus levels and will almost always be clinically ill.

Hypercalcemia of youth is seen in young dogs, up to 6-8 months in smaller dogs, and up to 1 year in larger breed/giant dogs. This is secondary to normal bone growth/remodeling. Calcium and phosphorus will both be elevated, with phosphorus being more out of reference range than calcium. These dogs are not ill.

Hypercalcemia can be seen in about 30% of dogs with Addison's disease. This is thought to be due to dehydration and pre-renal azotemia. These dogs are expected to have concurrent hyperphosphatemia, azotemia and "classic" electrolyte changes of hyponatremia/hyperkalemia. These patients will be ill, and the hypercalcemia/azotemia often quickly resolves with just aggressive fluid therapy (unlike true renal failure).

Renal failure can cause hypo, normal or hypercalcemia. Hypercalcemia is seen more commonly in

chronic, rather than acute renal failure. Even in chronic it is uncommon, being only seen in 14% of chronic renal failure cases. These patients are expected to have normal to high phosphorus levels, and will be variably clinically ill depending on the degree of azotemia. Hypercalcemia is generally seen with more advanced chronic renal failure (IRIS Stage III+, or creatinine >2.0).

Excessive Vitamin D can cause hypercalcemia and resultant renal failure. Vitamin D or analogs can be found in rodenticides (calciferols), health supplements/OTC vitamins and unexpectedly, as ointments for psoriasis. Vitamin D toxicity, unlike most other hypercalcemia causes, finds both significant hypercalcemia and hyperphosphatemia. This can result in severe renal failure (due to renal mineralization), GI and CNS signs. These animals will be ill unless caught in the very early stages prior to renal failure.

When elevated calcium is found on blood work, any elevation in calcium should not be ignored. Any hypercalcemia greater than 0.5 mg/dl above the reference range should be worked up further. Additionally, any persistent, milder elevations (above reference range for >2 weeks) or any patient that is ill should have the hypercalcemia investigated.

A very thorough history (travel history for granulomatous and any vitamin D exposure) and physical exam are essential for a dog with hypercalcemia. Special attention should be paid to the lymph nodes (lymphoma), rectal exam following anal sac expression (to assess the anal sacs for masses) and palpating for any mammary or intra-abdominal masses and palpating the spine/limbs for bone pain. Rarely, a neck mass can be palpated in the area of the thyroid in dogs with 1°PTH.

Following recheck of calcium (to eliminate spurious results), signalment, general bloodwork (CBC, chemistry and ideally urinalysis) and whether the patient is ill or not helps refine the list of differentials. The chemistry panel should help exclude: renal failure (if nonazotemic), Addison's disease (normal electrolytes, nonazotemic), and vitamin D toxicosis (if phosphorus is normal). Signalment (older, more likely neoplasia or 1°PTH) and illness status (not sick, more likely 1°PTH) will help further refine the differentials. Elevated globulins may suggest plasma cell tumor/Multiple myeloma or can be seen with pyogranulomatous infections.

If basic labwork does not identify the cause of hypercalcemia, the next step is measurement of iCa. This can be done more commonly in-house with point of care machines or as a sendout. Elevated iCa is commonly seen with 1°PTH, neoplasia, vitamin D toxicosis and osteoclastic disease. iCa is variably elevated with granulomatous disease and Addison's (~30% of the time), and it is rarely (6-10%) elevated and often low in renal failure.

Along with measurement of iCa, thoracic radiographs and abdominal imaging (ultrasound if available) should be pursued. These are looking for any masses, lymph node enlargement or urinary stones and radiographs help assess for any lytic bone lesions. Any masses should be aspirated (if safely reachable) and pulmonary miliary pattern with hilar lymphadenopathy should raise concern for fungal disease.

If a cause is still not identified, measurement of PTH should be pursued. PTH is measured through the lab at Michigan State, and iCa is always measured concurrently. Measurement of PTHrP can also be measured at the same time (a so called malignancy panel). Vitamin D levels can also be run if vitamin D toxicity is a concern. An elevated PTHrP is diagnostic for neoplasia (though it does not tell type), and an elevated iCa with a normal or elevated PTH is consistent with 1°PTH. PTH can also be elevated with renal failure, so this should be ruled out before submission. If changes consistent with 1°PTH are seen, or if the results come back ambiguous, an ultrasound of the parathyroid glands should be performed by a skilled ultrasonographer to look for a parathyroid tumor.

If no cause is still identified, consideration for aspiration of even normal-feeling lymph nodes and referral to a specialist should be strongly considered.

Treatment should be aimed at addressing the underlying cause of the hypercalcemia. Adjunctive therapies for patients with severe clinical signs of hypercalcemia or dangerously elevated tCa x Phos products include: IV fluid diuresis (0.9% NaCl preferred), furosemide (once hydrated) and if still refractory, bisphosphonates (such as pamidronate/alendronate). Corticosteroids can be very effective in decreasing calcium levels, but should be avoided until a definitive diagnosis has been made.

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About Our Organization

PVSES was founded to provide high quality, specialized medical care to companion animal patients. Our practice is dedicated to serving the veterinary community as a partner in total patient care. We offer comprehensive specialized services including endoscopy, Doppler ultrasound, surgery, 24-hour ICU care, and emergency and critical care. Our staff is committed to providing compassionate and thorough medical care that meets the needs of the patient, client, and referring veterinarian.

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