Hypercalcaemia in a Labradoodle

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You are presented with a 10-year-old female neutered Labradoodle weighing 21 kg (BCS 5/9). The owner reports a poor appetite, vomiting and increased thirst of 3 days' duration. The dog is up to date with preventative health care including vaccinations, endoparasite and ectoparasite control (Milbemycin Oxime and Afoxolaner, Nexgard Spectra, Boehringer-Ingleheim Animal Health UK Ltd and Praziqunatel, Droncit, Bayer). She is fed a good quality commercial dry dog food, has never travelled abroad, is not receiving any medication and does not have any significant previous medical history.

The dog was seen by a colleague 2 days previously for increased thirst and frequency of urination and had vomited once after food. Supportive treatment was provided (maropitant, Prevomax, Dechra Veterinary Products), and a urine sample was sent to an external laboratory for analysis including bacterial culture and sensitivity. The owner reports that the clinical signs have not improved; the dog is now very lethargic and the owner feels that the dog has lost weight.

Examination reveals a subdued mentation, mucus membranes are pink but tacky. Capillary refill time appears delayed (2–3 seconds). A skin tent can be elicited. The dog is panting. Heart sounds are audible, you do not detect a murmur or arrhythmia and record a heart rate of 112 beats per minute. Abdominal palpation is relaxed and does not reveal any areas of obvious discomfort or organomegaly. Rectal temperature is normal (37.8 °C).

Question 1 — Construct a problem list for this case.

Answer

- Polydipsia and polyuria: polydipsia not yet quantified by 24-hour water intake, but given the amount described and the presence of polyuria in the absence of lower urinary tract signs, considered true polyuria-polydipsia
- Vomiting
- Hyporexia
- Lethargy
- Weight loss
- Dehydration
- Reduced pulse quality.

Question 2 — What are the differential diagnoses?

Answer — Reduced appetite and lethargy are non-specific signs and can be attributed to many underlying causes.

Polydipsia/polyuria (PD/PU) may result from:

- Secondary nephrogenic diabetes insipidus (NDI) – this group presents multiple disease processes that are a major cause of the majority of PD/PU cases seen in practice. It includes but is not limited to the following:
  - Organ disease (chronic kidney disease (CKD), hepatic disease)
  - Endocrine disease (hypoadrenocorticism, hyperadrenocorticism)
  - Electrolytes abnormalities (hypercalcaemia)
  - Infectious causes (septicaemia, pyometra, bacterial pyelonephritis)
- Osmotic diuresis — diabetes mellitus, primary renal glucosuria, Fanconi syndrome, post-obstructive diuresis
- Medications — for example diuretics, phenobarbitone or glucocorticoids, which can be excluded in this case since the dog is not receiving any medications
- Psychogenic polydipsia with secondary polyuria — this is unlikely in view of the presentation of this dog as a sick patient
- Primary NDI – this is rare
- Central diabetes insipidus (CDI) — this is rare.

Vomiting may be primary gastrointestinal — acute gastritis including dietary indiscretion, foreign body, or extra-gastrointestinal — hypoadrenocorticism, hepatic disease, renal disease, pancreatitis, diabetic ketoacidosis, vestibular disease, toxins.

Weight loss could result from reduced food intake; this is a possible contributor in this case, as the dog is reported as having had a poor to absent appetite for a number of days. There could be increased nutrient loss via the gastrointestinal tract, e.g. protein-losing enteropathy or small intestinal disease with malassimilation of nutrients (to be considered given the vomiting), via the kidneys, for example, protein-losing nephropathy and Falconi syndrome, diabetes mellitus (glucose).

Weight loss could also result from an increase in energy usage: neoplasia (catabolic causes), others such as severe cardiac disease, pregnancy/lactation and excessive exercise can be excluded.

Question 3 — What do the haematology and biochemistry results show?

Answer — The haematology reveals an inflammatory leucogram (*Table 1*). Hypercalcaemia and hyperphosphataemia are present on the biochemistry panel (*Table 2*). Although compared with some parameters, the increase in calcium may seem mild, any increase in calcium should be considered significant and rechecked to assess whether the result is repeatable. There is a mild elevation in alanine aminotransferase (ALT) levels which could be attributable to either a primary hepatic disease or reflect a 'reactive hepatopathy' such as occurs secondary to gastrointestinal disease. At this stage you cannot exclude primary liver disease but consider it less likely given that ALT is only mildly increased, and there is minimal change in any other hepatobiliary parameters apart from a mild increase in bile acids. Elevations in creatinine kinase (CK) can indicate a myopathy but in this case CK was at a level generally not considered significant.

Question 4 — What is your interpretation of the urinalysis?

Answer — The urine specific gravity is 1.008 and therefore in the isosthenuric range (1.008–1.012). It supports the presence of PU/PD. Bacteria have been cultured (*Table 3*). Since voided urine samples have the potential for contamination by resident bacteria of the external genitalia and surrounding skin, and the patient was not demonstrating any clinical signs of lower urinary tract disease, the significance of the bacteriuria has to be questioned. To aid interpretation of the presence of bacteria in urine samples, bacteriuria is quantified as the number of colony forming units (CFU) per ml of urine. If the sample had been obtained by cystocentesis, a CFU of 10^3 would be considered as significant. However, in a voided sample such as in this case, less than 10^5 CFU/ml is interpreted as likely consistent with contamination rather than a true urinary tract infections. It is also now recognised that bacteriuria may be present in the absence of typical clinical signs of lower urinary tract disease. Based on evidence of protocols developed in human medicine, current recommendation is to monitor 'subclinical bacteriuria' and not to treat with antibiotics as part of sensible antibiotic stewardship (Weese et al, 2019). Therefore the use of antibiotics in this case was not supported.

Table 1. Haematology

Parameter	Result	Units and reference range
Red blood cells	7.03	$\times10^{12}$/l (5.9–8.4)
Haemoglobin	16.9	g/dl (14.2–20.0)
Haematocrit	51.7	% (43.0–60.0)
Mean corpuscular volume	73.5	fl (60.0–80.0)
Mean corpuscular haemoglobin	24	pg (22.0–25.9)
Mean corpuscular haemoglobin concentration	32.7	g/dl (30.8–35.5)
Red blood cell distribution	14.4	% (12.9–17.8)
Reticulocytes	24.6	$\times10^9$/l (20–151)
Platelets	208	$\times10^9$/l (108–562)
White blood cells	22.36*	$\times10^9$/l High (5.9–14.5)*
Neutrophils	76.0% 16.99*	$\times10^9$/l High (3.1–9.4)*
Bands	0.0% 0.00	$\times10^9$/l (0.0–0.3)
Lymphocytes	8.0% 1.79	$\times10^9$/l (0.8–4.7)
Monocytes	15.0% 3.35*	$\times10^9$/l High (0.0–1.6)*
Eosinophils	1.0% 0.22	$\times10^9$/l (0.1–1.4)
Basophils	0.0%, 0.00	$\times10^9$/l (0.0–0.2)
Blood Film Examination	Red cells appear normocytic and normochromic No abnormal white cells seen. Mild neutrophilia and a moderate monocytosis noted consistent with an inflammatory leukogram. Platelet morphology and numbers appear normal, with no evidence of platelet clumping or clots on the ethylenediamine tetraacetic acid smear	

*Abnormal results

Table 2. Biochemistry

Parameter	Result	Reference range and units
Total protein	73	54–77 g/l
Albumin	31	25–40 g/l
Globulin	42	20–47 g/l
Sodium	148	142–157 mmol/l
Potassium	4.8	3.6–6.6 mmol/l
Chloride	106	99–119 mmol/l
Calcium (total)	3.61*	2–3 mmol/l*
Phosphate	1.9*	0.8–1.6 mmol/l*
Urea	7.1	3–9 mmol/l
Creatinine	107	40–150 umol/l
Alkaline phosphatase (ALP)	72	0.1–150 U/l
Alanine aminotransferase	85*	5–66 U/l*
Total bilirubin	6.4	0.1–9 umol/l
Bile acids	10.7*	0.1–5 umol/l*
Glucose	5.3	3.5–6.5 mmol/l
Creatinine kinase	816*	0–190 U/l*
Cholesterol	6	3.8–7 mmol/l
Triglycerides	0.5	0.45–1.9 mmol/l
Amylase	912	1–1800 U/l
Lipase (DGGR)	40	0–100 U/l

*Abnormal results

Question 5 — What are the differential diagnoses for hypercalcaemia and hyperphosphataemia?

Answer — The most common causes of hypercalcaemia are shown in *Table 4*. A more comprehensive review of differential diagnoses can be found in texts listed in the further reading section and in Coady et al (2019) and Messinger et al (2009).

The causes of hyperphosphataemia include:

- Artefacts from haemolysis — none are noted here, and there is no evidence of changes on the haematology so this is an unlikely cause
- Reduced glomerular filtration — this can result from pre-renal, renal or post-renal causes. The history and presentation of this case allow you to immediately exclude urinary tract obstruction or rupture, and there is no azotaemia to support acute kidney injury or CKD. You consider whether the dehydration noted could be contributing, despite the absence pre-renal azotaemia, increased protein levels or haemoconcentration
- Diabetic ketoacidosis — this can be excluded because of the absence of hyperglycaemia or glycosuria
- Neoplasia — tumour lysis syndrome or osteolytic bone lesions
- Endocrine disease — nutritional or renal secondary hyperparathyroidism
- Toxic — vitamin D intoxication or cholecalciferol rodenticides.

Question 6 — You have the ability to measure ionised calcium (iCa) in the practice laboratory, and remember this is important to confirm true hypercalcaemia. Why do you do this?

Answer — The iCa result for this patient was 1.95 mmol/litre (1.0–1.45 mmol/litre). In general, ionised hypercalcaemia is usually the result of neoplastic disease, primary hyperparathyroidism or hypoadrenocorticism. CKD can result in total hypercalcaemia but rarely in ionised hypercalcaemia. Therefore when ionised hypercalcaemia and azotaemia are noted together, the latter should be considered the consequence of the ionised hypercalcaemia. In addition, dogs with primary hyperparathyoidism are typically well, and so the presence of ionised hypercalcaemia in an unwell dog should prompt concern over neoplasia and rapid pursuit of diagnostic investigations.

Ionised calcium is the biologically active form and is involved in feedback mechanisms to help maintain calcium within narrow parameters. Total calcium and iCa levels have been found to correlate poorly and therefore total calcium cannot be considered to reliably reflect iCa levels (Schenck and Chew, 2005). Blood samples need to be collected and processed correctly to ensure accurate measurement of iCa.

If the sample is collected aerobically and the serum allowed to mix with air, it favours binding of calcium to proteins and an increase in the pH of the sample and subsequent under-estimation of iCa levels (Schenck and Chew, 2008). It is therefore important to fill the serum blood collection tube sufficiently and run the sample without unnecessary delay. However, despite careful sample handling, spurious results can be obtained and the ability to analyse iCa in-house is advantageous to obtain an accurate and prompt result.

Table 3. Urinalysis

Parameter	Result
Collection method	voided (free catch)
Protein	+
pH	7
Blood	–
Glucose	–
Ketones	–
Urine specific gravity (refractometer)	1.008
Urine culture and sensitivity panel	30 000 cfu/ml *Staphylococcus pseudointermedius*
	Antibiotic sensitivity
	Ampicillin – resistant
	Pot amoxycillin – sensitive
	Cephalexin – sensitive
	Cefovecin – sensitive
	Tetracycline – resistant
	Pot sulphonamide – sensitive
	Enrofloxacin – sensitive
	Marbofloxacin – sensitive

Table 4. Common causes of hypercalcaemia

Cat	Dog
Idiopathic (20–25%)	Neoplasia (lymphoma, apocrine gland adenocarcinoma)
Chronic kidney disease (20%)	Primary hyperparathyroidism
Malignant neoplasia associated (20%)	Chronic kidney disease
Vitamin D toxicosis/ hypervitaminosis D	Hypoadrenocorticism
Granulomatous disease	Vitamin D toxicosis/ hypervitaminosis D
	Granulomatous disease

Question 7 — What is your initial management plan for this case?

Answer — Hypercalcaemia is a sign and not a diagnosis in itself. Initial management aims, in a patient presenting acutely unwell with hypercalcaemia, are therefore to stabilise the patient and ameliorate the clinical signs, by addressing the identified problems, before performing further diagnostics to identify the cause of the hypercalcaemia (*Box 1*). Patients in a hypercalcaemic crisis are typically very dehydrated and therefore an estimation of dehydration should be used alongside ongoing fluid losses and maintenance requirements to accurately calculate fluid requirements (*Box 2*).

Question 8 — How would you investigate this case further?

Answer — At this stage you have established that you have a case of hypercalcaemia and a differential diagnosis list for the

Box 1. Management steps for patients presenting acutely unwell with hypercalcaemia

Primary treatments

- Diuresis (calciuresis) and rehydration:
  - Intravenous fluid therapy should be instituted. The aim is to initially rehydrate the patient to correct fluid deficits and then to promote calciuresis. Fluid rate will therefore depend on percentage dehydration at presentation and adjustments for ongoing losses
  - Dehydration leads to haemoconcentration which results in a decrease in glomerular filtration rate in the kidney. Consequently, calcium excretion is decreased. Isotonic saline (0.9% NaCl) is generally considered most appropriate for hypercalcaemic patients since it does not contain calcium ions and also promotes competitive inhibition of calcium with sodium ions for resorption in the renal tubules. Electrolytes should be monitored to avoid hypernatraemia and hypervolaemia should be avoided.
- Furosemide (loop diuretic):
  - Furosemide 1–2 mg/kg IV, IM, PO q 8–12 hours. Readers may choose to refer to the protocol listed in the BSAVA Small Animal Formulary (9th edition) (Ramsey, 2017) which lists a method involving a bolus and then ongoing treatment. Doses are higher than listed above
  - Hydrate first.
- Glucocorticoids:
  - Dose recommendations vary depending on reference. A dose of 1–2 mg/kg daily has been recommended, although this should not be maintained for long periods but tapered to 0.5 mg/kg q 12 hours.
  - Steroids can interfere with establishing a diagnosis, such as falsely decreasing parathyroid hormone-related peptide (PTHrp) levels and affecting cytology/biopsy sample interpretation. Glucocorticoid therapy should ideally only be used after a diagnosis has been obtained. Alternatively they may be initiated after all investigations that could be affected by glucocorticoids have been performed or following a careful discussion with the owner in the scenario that further investigations have been declined and a palliative route adopted.
  - Effects of glucocorticoids include:
    - Decreased bone resorption via inhibition of osteoclast maturation
    - Diminished number of calcitriol receptors present in bone
    - Impeded intestinal Ca absorption
    - Increased renal Ca excretion
    - Vitamin D antagonism has also been observed with the use of glucocorticoids.

Secondary treatments

- This includes the use of bisphosphonates, sodium bicarbonate and calcitonin (which inhibits osteoclast activity). These additional possible therapies are considered to be secondary treatments, generally used in the chronic rather than acute management of hypercalcaemia. Calcitonin is the exception, as it is available as an injection and therefore typically used in the acute setting.
- Bisphosphonates:
  - Bisphosphonates decrease osteoclast activity and encourage osteoclast apoptosis. The bisphosphonates zoledronate and pamidronate are now standard of care in management of hypercalcaemia in people. The effectiveness of pamidronate in dogs and cats has been demonstrated (Hostuler et al, 2005) and more recently zoledronate has also been shown to be effective in the management of hypercalcaemia in a small group of dogs (Schenk et al, 2018).

most likely causes in a dog. You refine this list by excluding kidney disease, based on the blood results, and vitamin D toxicosis following discussion with the owner. The latter is considered very unlikely since the dog has not had any known access to vitamin pills, cholecalciferol rodenticides or psoriasis creams that can be high in vitamin D. Granulomatous disease in the UK is rare, especially in a dog that has not travelled abroad and you think hyperparathyroidism is less likely because of the severity of the clinical signs. You are concerned about a neoplastic process.

Further investigation at this stage will depend on your skill level, practice facilities and owner funds and expectations and may involve obtaining advice from, or referral to, a multidisciplinary referral centre.

Further investigation of hypercalcaemia may include some or all of the following:

- Survey imaging (radiography and ultrasound)
- Assessment of the anal glands to rule out a mass that could be consistent with an anal gland adenocarcinoma
- Ultrasound and/or computed tomography (CT) scan of the cervical region to evaluate the parathyroid gland
- Collection of blood samples for measurement of parathyroid hormone (PTH) to assess parathyroid gland function and parathyroid hormone-related peptide (PTHrp) for evaluation of paraneoplastic hypercalcaemia
- Sampling of any masses identified
- Advanced imaging to provide further information on any findings from survey imaging

You have access to digital radiography and ultrasonography and therefore decide to perform some diagnostic imaging now the dog is more stable. The investigations performed in this case included:

- Palpation of anal sacs under sedation before imaging – this did not reveal an apocrine gland mass

Box 2. How to calculate fluid requirement based on percentage dehydration

- Patient weight 21 kg
- Aim to replace the losses over 24 hours
- Maintenance requirements: generally accepted as 40–60 ml/kg/day which equates to 1.6–2.5 ml/kg/hr. Therefore in practice, 2 ml/kg/hr is often used as an easy approximation
  2 × 21 kg=42 ml/hr=1008 ml over 24 hours
- Volume to correct for dehydration: percentage dehydration×body weight=volume (l)
  7% 7/100 × 21 kg=1.47=1470 ml to replace
- Add the two together: 1008 + 1470=2478 ml over 24 hours, *103 ml/hour* (5 ml/kg)
- A decision will need to be made as to whether the patient is purely dehydrated, or whether there is evidence of hypovolaemia which can occur with, for example, severe dehydration and polyuria. If hypovolaemia is present, fluid boluses will be required before addressing dehydration and maintenance requirements. Further information can be found in the further reading section.

- Thoracic and abdominal radiography – revealed a mediastinal mass and a number of areas of patchy increase in opacity overlying the lung fields
- Thoracic ultrasonography – this is being used more widely in the veterinary profession with development of Thoracic Focused Assessment with Sonography in Trauma (T-FAST) and Vet Bedside Lung Ultrasound Examination (Vet BLUE), which has moved the technique to include critical patients beyond those with trauma. A full description is beyond the scope of this article, see *Further reading* section. A mediastinal mass with cystic pockets measuring approximately 3.5 × 5.5 cm was noted extending from the thoracic inlet cranial to the heart and closely associated with the blood vessels. 'B lines' were noted within the lung fields.
- Abdominal ultrasound – unremarkable
- CT of the thorax
- Ultrasound-guided fine needle aspirate (FNA) cytology sample collection from the thoracic lesion
- PTH/PTHrP bloods – these were taken but not run. The results of imaging and cytology from the thoracic mass were known and therefore the results would not have added significantly to the diagnosis to justify the additional costs that would have been incurred.

Radiograph images are shown in *Figures 1* and *2*.

Question 9 — Given the results of tests performed, what is your working diagnosis?

Answer — The main differential diagnosis of the thoracic mass in this case were lymphoma and thymoma.

Question 10 — What further investigations might you carry out if funds are available?

Answer — Sampling the mass for cytology or histopathology will provide further information about the nature of the mass. Cytology, such as obtained in this case, using ultrasound-guided FNAs has the advantage of being less invasive and providing a faster result than biopsy. Lymphoma generally exfoliates well, but the sample retrieved by FNA may be too small or poorly cellular and therefore the possibility of an inconclusive result

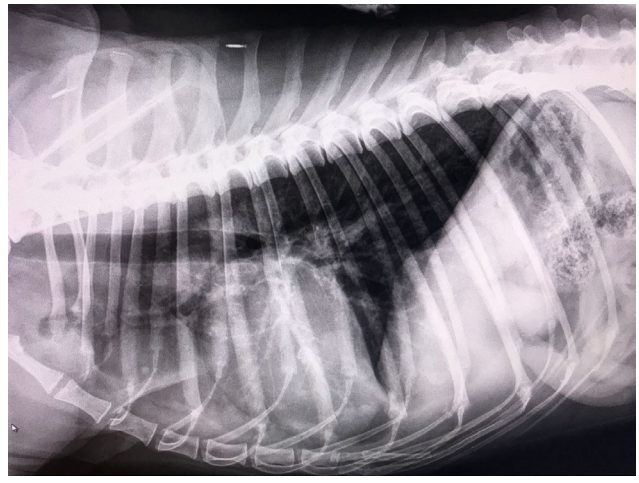

Figure 1. Right lateral thoracic radiograph showing a oval shaped area of increased opacity cranial to the cardiac outline consistent with a mass and a number of areas of patchy increase in opacity overlying the lung fields

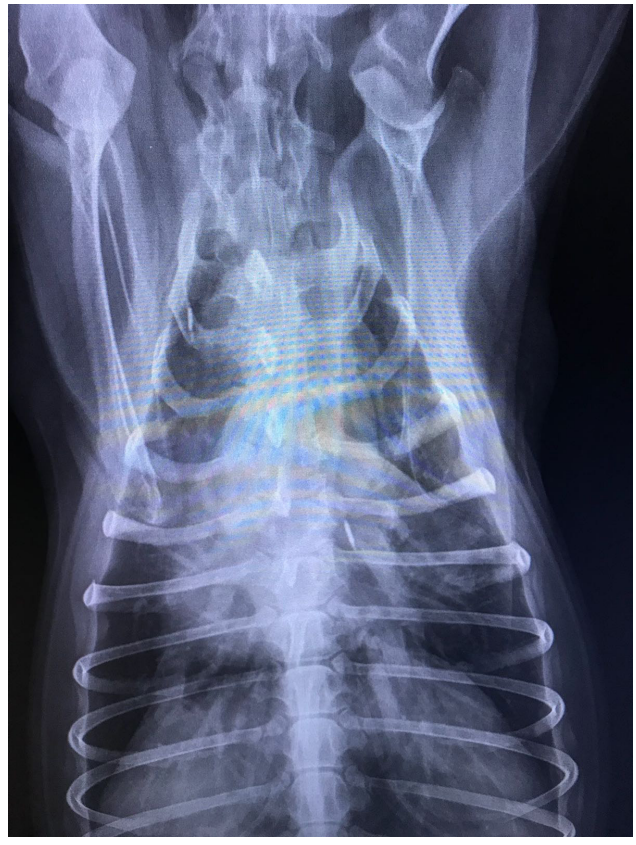

Figure 2. Dorsoventral thoracic radiograph demonstrating patchy alveolar pattern in cranial lung fields

should be discussed with the owner. Biopsy collection is more invasive; the mass was positioned in the thorax close to the heart. Consequently, this technique may not be as accessible in general practice and carries a greater risk of complication. Thoracic CT can be performed to assess the extent of the mass and suitability for surgical resection, and for evidence of metastatic change.

Questions 11 — Following all the investigations, what is your final diagnosis?

Answer — The FNA results were consistent with malignant thymoma. A good prognosis with surgery has been reported, even where there is an associated paraneoplastic hypercalcaemia (Robat et al, 2013). Therefore the dog underwent thoracic CT to evaluate metastatic spread and to allow for surgical planning. Unfortunately, CT demonstrated invasion within the mediastinal and pleural tissues and metastasis to thoracic lymph nodes meaning that complete surgical resection was not possible. Supportive management, including use of anti-emetics, and management of the hypercalcaemia with glucocorticoids and bisphosphonates, was discussed. However, in view of the poor prognosis and deteriorating clinical status of the patient, the dog was euthanised a few days after definitive diagnosis was obtained.

Discussion

Calcium is involved in a wide range of cell functions including the coagulation cascade, muscle contraction, vascular smooth muscle tone, hormone secretion, regulation of cell growth, neuromuscular transmission and various enzyme activity. It is therefore vital that calcium is regulated efficiently to avoid the consequences that would occur from a deviation from the normal range (*Box 3*).

Calcium is tightly regulated within the body by a number of feedback mechanisms primarily involving the PTH and calcitriol (active form of vitamin D3), but also other substances including calcitonin and feedback from blood calcium and phosphate levels. PTH is produced in the chief cells of the parathyroid gland and secreted in response to hypocalcaemia. In patients with humoral hypercalcaemia of malignancy or vitamin D toxicosis, PTH level would be expected to be low. If PTH is normal or high in the face of hypercalcaemia it indicates an autonomously active gland and hyperparathyroidism.

Hypercalcaemia can be readily identified on a biochemistry panel, and identification of hypercalcaemia should prompt further investigation to confirm that the result is not spurious and that the elevation is persistent. The hypercalcaemia in this case is an example of a paraneoplastic syndrome: the indirect effect of the tumour resulting from release of biologically active substances such as hormones, growth factors and cytokines.

Thymoma is a less common cause of malignancy-associated hypercalcaemia, with an incidence of 0.9% in one study (Coady et al, 2019) with lymphoma recognised as the most common cause (Messinger et al, 2009; Coady et al, 2019). A number of paraneoplastic syndromes have been associated with thymoma, including myasthenia gravis and megaoesophagus (Robat et al, 2013). The paraneoplastic syndrome may be the first evidence of, and be more debilitating than, the underlying disease process and therefore requires addressing concurrently to the underlying neoplasia (Elliott, 2014).

In acutely sick patients, where malignancy is suspected, diagnostic imaging should be performed as a priority rather than waiting for results of blood analysis of PTH and PTHrP (Elliott, 2014). PTH/PTHrP tests typically have a delayed turnaround time and are costly. Diagnostic imaging and, where appropriate, tissue sample collection will be more useful in elucidating the underlying cause in this case. Sonography of the cranial mediastinum, in the presence of a mediastinal mass or pleural/mediastinal fluid, is considered a sensitive method of assessing mediastinal disease and a valuable addition to radiography. In addition, ultrasound-guided biopsy or aspirate are recognised as augmenting a diagnosis made on imaging (Konde and Spaulding, 1991).

Cytology may not always be as reliable as histopathology in supporting a diagnosis, but carries the advantage of being a less invasive method. With respect to cytology from thoracic masses, Pintore et al (2014) reported 'good correlation of cytology with histopathology' and pointed out the benefit of cytology being a 'speedy result in sick patients'. Robat et al (2013) similarly found 95% agreement between cytological and histopathological samples, supporting the use of FNAs in this case. In addition, flow cytometry can be performed on tumour aspirate samples as a reliable method of differentiating mediastinal lymphoma from thymoma without the need for more invasive methods (Lana et al, 2006).

Even in the absence of sample collection, the ultrasonographic appearance of the mediastinal mass may provide an idea of whether thymoma or lymphoma is most likely. A heterogeneous

Box 3. Why is calcium so closely regulated?

- Reviewing the consequences of derangements in calcium levels provides an appreciation of the mechanisms behind the expected clinical signs of a patient with significant hypercalcaemia (Barber, 2001; Daniels and Sakakeeny, 2015)
- Risk of soft tissue mineralisation, particularly the kidneys and subsequent decline in function (metastatic calcification)
- Development of calcium oxalate uroliths and risk of urinary tract obstruction (especially cats)
- Cellular dysfunction
- Cardiac arrhythmias (effect on the action potential)
- Gastrointestinal effects of anorexia, vomiting and constipation as a consequence of reduced smooth muscle contractility
- Neurological signs including muscle twitching and seizure activity
- Lethargy and weakness as a result of reduced neuromuscular activity
- Development of nephrogenic diabetes insipidus: renal resistance to effect of vasopressin — resulting in polydipsia/polyuria and a reduction in urine specific gravity.

echogenic or cystic mediastinal mass increases the clinical suspicion of thymoma compared with lymphoma. The lack of cysts or heterogeneous echogenicity increases the suspicion of lymphoma (Patterson and Marolf, 2014).

Thymomas are described as locally invasive, as in the dog in this case, or benign, but rarely metastasise to distant sites. There are different histological subtypes of thymoma, including lymphocyte-rich which is considered to carry a better prognosis. However, the presence of lymphocytes can sometimes make differentiation of lymphoma from thymoma on cytology difficult. Determining whether lymphoma or thymoma is present is important, since treatment of lymphoma is typically medical, whereas thymomas are considered surgical. Some clinicians use the response to a trial of chemotherapy for lymphoma as a method of differentiating lymphoma from thymoma where the diagnosis remains unclear. Failure to respond within 14 days makes thymoma more likely and the possibility of surgical resection should be reviewed. Where resection of the thymoma is possible, a medium survival time of 635–790 days have been reported in dogs, which is significantly higher than when surgery is not performed. Excision is considered an effective treatment option for thymoma, although, as in the case discussed here, surgery may not be feasible because of extensive invasion of the tumour or risk of damage to surrounding thoracic structures (Zitz et al, 2008; Robat et al, 2013).

Conclusions

A logical approach to investigation of hypercalcaemia is required to identify, treat and, where possible, eliminate the underlying cause. Any increase in calcium on a biochemistry profile should be considered significant and a repeat sample run to assess whether the result is true and persistent or spurious. A persistent result should be investigated further.

Some dogs with hypercalcaemia may be acutely sick, and stabilisation before and during diagnostic tests should not be forgotten. Treatment of hypercalcaemia is recommended even if there are no clinical signs at the time of diagnosis, such as with a well dog with primary hyperparathyroidism, to avoid the inevitable longer term adverse effects of hypercalcaemia.

There are a number of underlying causes of hypercalcaemia, with little agreement on the exact frequency of each cause. However, neoplasia is considered the most likely cause in the dog, especially when accompanied by more severe clinical signs. Therefore, hypercalcaemia in an unwell dog should prompt use of diagnostic imaging and palpation of the anal glands to identify the underlying neoplasm.

The most common causes of a mediastinal mass with paraneoplastic hypercalcaemia are lymphoma and thymoma. Diagnostic imaging including radiography and ultrasonography, and CT where available, are all useful in further identifying and further assessing mediastinal masses. FNA cytology can provide further useful information to assist decision making in these patients. However, it can be difficult to differentiate thymoma from lymphoma as some thymomas can be very rich in lymphocytes. Although hypercalcaemia does not appear to be associated with a worsening prognosis for dogs with mediastinal thymoma, and surgery can result in some favourable outcomes, prognosis is guarded overall. CA

Conflict of interest:
None.

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