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CASE REPORT

Companion or pet animals

Splenic lymphoid hyperplasia in a cat presenting with hyperammonaemia, hypercalcaemia and hypercobalaminaemia

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Abstract

A 5-year-old, male neutered, Bengal-cross cat presented with progressive neurological signs (ataxia and torticollis). Initial haematology, serum biochemistry and electrolytes (including calcium) were unremarkable; however, ammonia was markedly elevated. Portosystemic shunting and hypocobalaminaemia were ruled out (cobalamin levels were markedly elevated) and there was no organic aciduria. Hyperammonaemia was medically managed, but later, seizures developed, at which time the cat was found to have severe hypercalcaemia. Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) levels decreased. Computed tomography angiography demonstrated unusual contrast uptake within the spleen ('zebra-stripes'). Histopathology of the spleen demonstrated diffuse lymphoid follicular hyperplasia. Post-splenectomy, hypercalcaemia and hyperammonaemia both resolved (hypercobalaminaemia persisted). The cat remained bright and well after 8 years of splenectomy.

This is the first report of hypercalcaemia associated with splenic lymphoid hyperplasia. In this case, both PTH and PTHrP were low, suggesting that hypercalcaemia was mediated via an alternative mechanism.

BACKGROUND

Hypercalcaemia remains a relatively poorly understood finding in feline medicine. Studies assessing ionised calcium levels have reported a number of aetiologies, including acute kidney injury, malignancy induced, idiopathic, chronic renal disease/diet, primary hyperparathyroidism, vitamin D toxicity and granulomatous disease.[1] There are reports of additional causes in other species, including endocrinopathies such as thyrotoxicosis, hypoadrenocorticism, hypercalcaemia induced by therapeutics (milk-alkali syndrome, hypervitaminosis A or thiazide diuresis) and inherited disorders, such as hypocalciuric hypercalcaemia.[2,3] Rare causes of hypercalcaemia are noted including increased levels of calcitriol in neoplastic and granulomatous diseases, bartonellosis, Crohn's disease and lipoid pneumonia and hypercalcaemia of unknown aetiology, which has been associated with granulomatous diseases, cytomegalic virus infection in AIDS, *Nocardia* pericarditis, brucellosis, lymphoedema in systemic lupus erythematosus and lymphadenopathy with high interleukin-6.[3] Finally, infection with the retrovirus, human T-cell lymphotrophic virus-1 (HTLV-1) has been associated with hypercalcaemia (both in patients with and without associated neoplasms).[4] This can be mediated by increased levels of parathyroid hormone-related peptide (PTHrP) and calcitriol or by upregulation of receptor activator of nuclear factor-kappa B ligand (RANK-L).

This report documents hypercalcaemia, hyperammonaemia and hypercobalaminaemia in a cat with splenic lymphoid hyperplasia. The mechanisms for the development of hypercalcaemia and hyperammonaemia were not identified; however, both resolved after removal of the spleen.

CASE PRESENTATION

An indoor/outdoor, 5-year-old, male neutered Bengal-cross cat was initially presented to the referring veterinarian for lethargy, dehydration and suspected nausea, without overt neurological abnormalities at that time. The cat lived in England and had no history of overseas travel. The only significant prior illness was a single episode of mycoplasma pneumonia 2 years earlier.

The cat was well grown and in good body condition. Initial haematology and serum biochemistry demonstrated mild haemoconcentration (HCT 48.6%, reference interval [RI] 30%–45%), with no other significant abnormalities; total calcium was within reference limits (9.7 mg/dL, RI 7.8–11.3 mg/dL).

Despite intravenous fluid therapy, the clinical signs progressed over the subsequent 24 hours to include ataxia, a wide-based stance and head tremors, at which point the referring veterinary surgeon suspected bilateral otitis media and initiated treatment with amoxicillin–clavulanate and meloxicam (Table 1). Although there was initial mild improvement, the cat later deteriorated, developing episodic non-ambulatory ataxia, a left-sided head tilt, and horizontal nystagmus (fast phase to the right), prompting referral for further investigation.

Clinical examination demonstrated a grade II/VI systolic heart murmur, wide-based stance and episodic torticollis. Otoscopic and retinal examinations were unremarkable. A complete neurological examination was not completed due to the cat's demeanor. The systolic blood pressure (Doppler technique) was elevated at 170 mmHg; the increase was attributed to stress, with later assessments demonstrating normotension (130 mmHg). Brief echocardiographic examination demonstrated a trivial jet of mitral insufficiency but no other abnormalities. Complete blood count (CBC) and serum biochemistry did not demonstrate any abnormalities. Screening was performed for infectious diseases (*Toxoplasma* serology* [IgG and IgM]; antibody testing for feline immunodeficiency virus*; antigen testing for feline leukaemia virus*; Leptospiral PCR on blood and urine*). These were negative, with the exception of the blood PCR for leptospiral organisms, which was positive, despite a negative urine PCR. Fasting bile acid (BA)* and ammonia* were assessed. The fasting BA was 1.6 µg/mL (RI 0–5.9 µg/mL) and the fasting ammonia was 823.5 µg/dL (RI 0–85 µg/dL)†. In light of the hyperammonaemia, the cat was started on lactulose and levetiracetam. The amoxicillin–clavulanate was continued, and he was changed to a restricted protein (renal) diet. The differentials for hyperammonaemia were considered to be portosystemic shunt (PSS), severe hepatic dysfunction, hypocobalaminaemia or errors of urea metabolism (resulting in organic aciduria). To investigate these, a BA stimulation test (BAST), cobalamin levels* and an abdominal ultrasound were performed. The BAST was within reference limits (pre: 0.6 µmol/L and post: 0.0 µmol/L, RI 0–15). Hypocobalaminaemia was excluded (the cobalamin level was markedly increased to >1000 ng/L, RI 298–678 ng/L). Abdominal ultrasonography performed by a diplomate of the European College of Veterinary Diagnostic Imaging (DipECVDI) demonstrated no abnormalities; the liver was normal in size, with normal parenchyma, and the portal vein did not demonstrate any abnormalities. Furthermore, the spleen, gastrointestinal tract and urinary tract were all considered normal in appearance. A urine sample was obtained, and routine urinalysis demonstrated no abnormalities; the specific gravity was 1.050, and pH was 7.5. The sample was submitted for organic aciduria‡, which did not demonstrate any abnormal metabolites.

Magnetic resonance imaging (MRI), including T1-weighted, T2-weighted and fluid-attenuated inversion recovery imaging, was performed. MRI was assessed by a DipECVDI; no gross abnormalities were detected within the brain or the extra-cranial structures. A cerebral spinal fluid (CSF) tap was submitted for analysis*, the tap was acellular, and the volume was too low to assess protein content. Pan-bacterial PCR* of the CSF was negative; therefore, it was considered that hyperammonaemia was most likely the cause of the neurological abnormalities, and the positive blood leptospiral PCR was considered an incidental finding.

LEARNING POINTS/TAKE HOME MESSAGES

- This case raises more questions than it resolves and highlights gaps in our current understanding of the aetiology of feline hypercalcaemia.
- While the case fulfils the diagnostic criteria for idiopathic hypercalcaemia, the complete and sustained resolution following splenectomy raises the possibility that the associated lymphoid hyperplasia may have contributed to the development of hypercalcaemia.
- Hypercobalaminaemia has been reported in association with inflammatory disease in cats; however, in this case, elevated cobalamin concentrations persisted despite resolution of other clinical and laboratory abnormalities.
- All recognised causes of hyperammonaemia in cats were excluded in this case, yet the patient exhibited prolonged hyperammonaemia of unknown origin, suggesting that additional, as yet unidentified, aetiologies may exist.

Initially, the cat improved on medical management for hyperammonaemia (Table 1), with episodic relapses after hunting mice or steeling food. However, 2 months after initiating therapy for hyperammonaemia, the cat suddenly deteriorated. He presented with marked torticollis, he was vacant and anorexic, and demonstrated what the owner described as 'robotic walking'. He had a marked left-sided head tilt, and facial twitching, licking and muscle fasciculations, suggesting seizure activity. A CBC*, serum biochemistry* and venous blood gas§ were obtained. This demonstrated marked hypercalcaemia (ionised calcium 1.74 mmol/L, RI 0.9–1.33 mmol/L), but no other abnormalities (phosphorus was 3.75 mg/dL, RI 2.9–4.8 mg/dL*). The cat was placed on intravenous fluids (Hartmann's solution) supplemented with a vitamin B complex (Table 1). In addition, phenobarbitone therapy was initiated, with a 12 mg/kg intravenous bolus, followed by two 5 mg/kg boluses at 20-minute intervals. There was a good response to therapy; the seizure activity abated, although the head tilt and occasional episodes of torticollis remained. The cat started eating and his demeanor improved. Phenobarbitone therapy was continued at 2 mg/kg per os, every 12 hours. The ionised calcium fluctuated between 1.66§ and 1.56 mmol/L§ over the next 4 days. Alendronate therapy was initiated; after a 6-hour fast, 10 mg of alendronate was administered per os, followed by 5 mL of water. At this point, further investigations were delayed due to financial restrictions. The cat was maintained on medications (Table 1) and the ionised calcium was monitored (Figure 1). The levels continued to fluctuate despite medications (alendronate and later prednisolone). Initially, the cat remained on a renal diet, but the formulation and manufacturer were altered. This was withdrawn 3 months after the onset of hypercalcaemia.

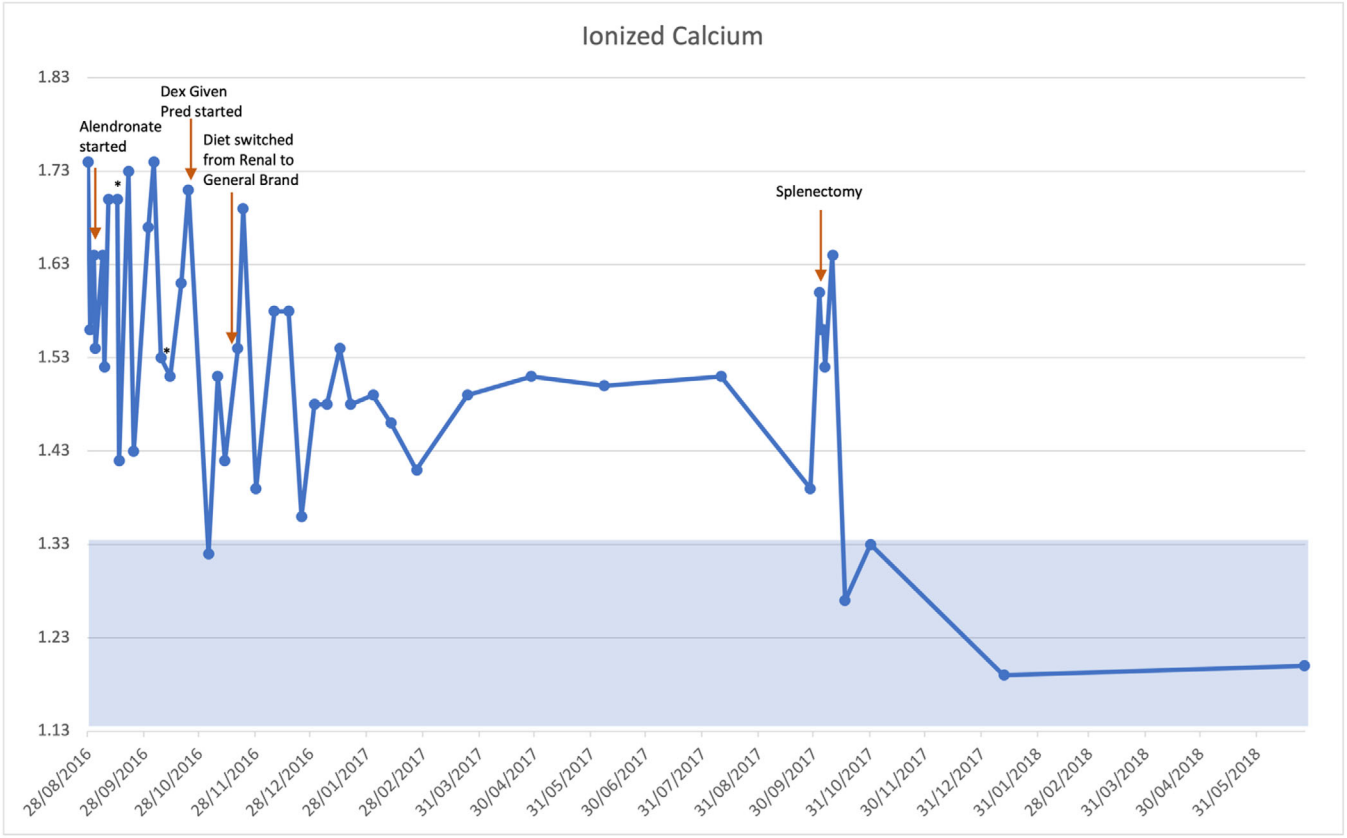
TABLE 1 Medications administered to the cat throughout the duration of treatment.

Date	Medication	Dosage	Duration	Reason
12/04/2016	Amoxicillin–clavulanate (Clavapet, MiPet)	50 mg bid po (9.3–10.9 mg/kg)	20 months	Started for otitis media, but continued when hyperammonaemia diagnosed
12/04/2016	Meloxicam (Metacam Boehringer Ingelheim)	0.1 mg/kg sid po	1 week	Prescribed for suspected otitis media
10/06/2016	Maropitant (Cerenia, Zoetis)	1 mg/kg once s/c	Once	Prescribed for suspected vestibular disease
15/06/2016	Lactulose (Generic)	2 mL (3.35 g/5 mL solution) tid po	18 months	Treatment for hyperammonaemia
15/06/2016	Levetiracetam (Generic)	100 mg tid po (18.5–20.8 mg/kg)	18 months	Included in treatment for hyperammonaemia and later for seizure
28/08/2016	Phenobarbitone (Epiphen, Vetoquinol)	7.5 mg bid po (after loading) (1.4–1.5 mg/kg)	16 months	Treatment for seizures
31/08/2016	Alendronate (Generic)	10 mg once weekly po, increased to twice/week 13/9/16 and eod 12/10/16	16 months	Treatment for hypercalcaemia
31/08/2016	Potassium chloride (Generic)	7 mEq/500 mL delivered iv at 16 mL/h CRI	48 hours	Administered while receiving iv fluids post-seizures
31/08/2016	Vitamin B complex (Combivit, Norbrook)	2.5 mL diluted into 500 mL: administered at 10 mL/h iv 1 mL supplement containing: 35 mg thiamine hydrochloride, 0.5 mg riboflavin sodium phosphate, 7 mg pyridoxine hydrochloride, 23 mg nicotinamide, 70 mg ascorbic acid	48 hours	Supplemented post-seizure activity
22/10/2016	Dexamethasone (Vetoquinol)	0.2 mg/kg once s/c	1 injection	Treatment of refractory hypercalcaemia
23/10/2016	Prednisolone (Prednicare, AnimalCare)	5 mg sid po (0.9–1.1 mg/kg)	12 months	Treatment of refractory hypercalcaemia

Abbreviations: bid, twice daily; CRI, constant rate infusion; eod, every other day; iv, intravenous; s/c, subcutaneous; sid, once daily; tid, three times daily.

There was no alteration in the hypercalcaemia with dietary changes. Once finances permitted (6 months later), further investigations were pursued. To investigate potential causes of hypercalcaemia, blood was submitted for biochemistry profile*, parathyroid hormone (PTH) and PTHrP. Both PTH and PTHrP were below the detectable limits of the assay (PTH < 10.0 pg/mL, RI < 40 pg/mL||; PTHrP < 0.1 pmol/L, RI < 0.5 pmol/L||); at that time, ionised calcium was 1.51 mmol/L (RI 1.13–1.33 mmol/L§). In addition, ammonia remained elevated at 314 μg/dL (RI 0–85 μg/dL*) and cobalamin was 1439 ng/L (RI 313–836 ng/L¶). In order to re-assess for a PSS, granulomatous disease or myeloma-related disorder, quadriphasic contrast-enhanced computed tomography (CT) was performed. The CT was assessed by a DipECVDI; no lesions were identified within the musculoskeletal system. There was a mild thickening of the bronchial walls, but no other thoracic lesions. Within the abdominal cavity, the size of all the portal vein tributaries was normal, with a normal anatomical ramification and distribution of the portal vein divisions. The liver was of normal size and density. The spleen demonstrated a very heterogenous post contrast enhancement, with a 'zebra-striped' appearance, present on both the early and delayed venous series (Figure 2). In addition, a small nodule was evident on the medial aspect of the spleen. No other abnormalities were identified.

In light of the diffuse nature of the lesions noted on CT, splenectomy was advised. Pre-operative bloodwork demonstrated that the haematocrit was 35%. A premedication of 0.3 mg/kg of methadone was administered intramuscularly, followed by intravenous induction with propofol. Additional analgesia was provided in the form of a morphine epidural and midline coeliotomy and the abdominal contents were examined. No gross abnormalities were identified. The splenic bursa was opened, the vessels along the splenic hilus were ligated and the spleen was removed. The spleen was submitted for histopathology and aerobic and anaerobic culture*. Post-operative pain scores were performed at 4 hourly intervals, and instructions were given to administer 0.2 mg/kg methadone if there was an increase (this was not required). The haematocrit remained stable (post-operative HCT 33%). Cultures of the spleen were negative. Histopathology# was initially thought to be consistent with mantle cell lymphoma, but immunohistochemistry demonstrated moderate diffuse lymphoid follicular hyperplasia with distinct populations of T and B lymphocytes extending within the periarteriolar lymphoid sheaths (Figure 3). PCR for antigen receptor rearrangement (PARR) testing** revealed polyclonal T- and B-lymphocyte antigen receptor rearrangements, again consistent with lymphoid hyperplasia rather than lymphoma. There was no evidence of a granulomatous inflammatory process within the spleen.



Legend: * represents increases in alendronate dosage; Dex, Dexamethasone; Pred, Prednisolone

FIGURE 1 Calcium fluctuations from diagnosis of hypercalcaemia until resolution. Abbreviations: Dex, dexamethasone; Pred, prednisolone.

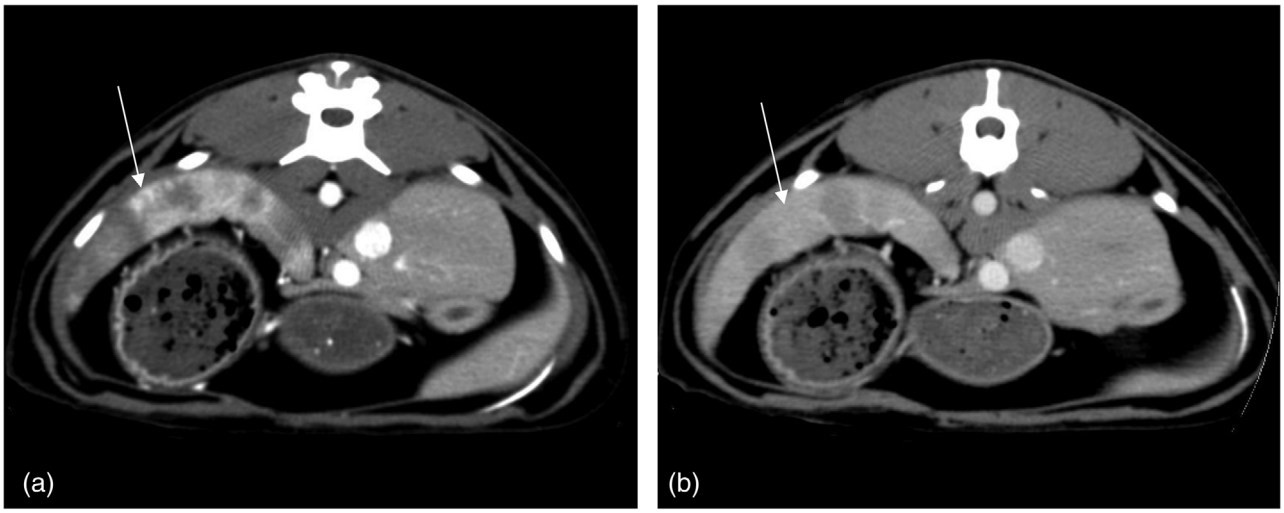


FIGURE 2 Computed tomography (CT) images. CT axial section at the level of the mid abdomen demonstrating (a) dual-phase and (b) late-phase angiography. The heterogenous appearance of the splenic parenchyma after contrast administration can be seen.

OUTCOME AND FOLLOW-UP

Post-operatively, the cat demonstrated a marked improvement; the ionised calcium decreased and normalised over the following 2 weeks. Alendronate therapy was discontinued and prednisolone was tapered and discontinued over an 8-week period. Initially, both the ammonia and cobalamin remained elevated. However, as clinical signs resolved, the other treatments were gradually discontinued. At re-assessment, 6 months post-splenectomy, the ammonia had normalised (71 μg/dL, RI 0–85 μg/dL*), although the cobalamin remained elevated (>1000 ng/L, RI 298–678 ng/L*).

The cat has been followed for over 8 years since splenectomy (he is currently 15 years of age). There has been no recurrence of the clinical signs, and both ionised calcium and ammonia have remained within RIs. There have been no long-term negative consequences from the splenectomy.

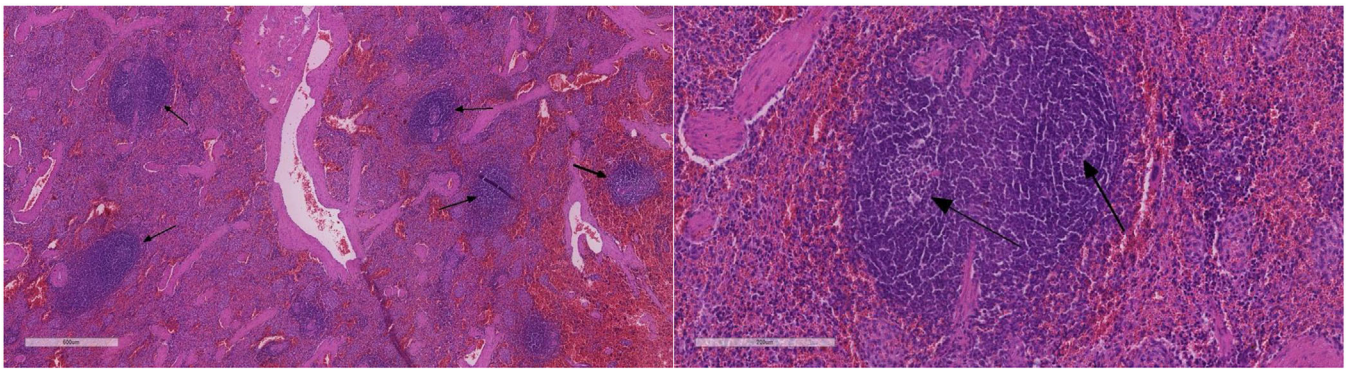


FIGURE 3 Haematoxylin and eosin-stained sections of the spleen. (a) Arrows demonstrate the periarteriolar lymphoid sheaths and (b) arrows demonstrate the germinal centres of the hyperplastic periarteriolar lymphoid sheaths. The presence of the germinal centres confirm a hyperplastic process.

DISCUSSION

This report documents the first case of hypercalcaemia in a cat with splenic lymphoid hyperplasia. Splenic lymphoid hyperplasia is most commonly associated with infectious diseases.[5] In this case, no infectious aetiology was identified despite culture and retroviral screening and there was no evidence of a splenitis on histopathology. Resolution of the hypercalcaemia post-splenectomy suggested that the disease was isolated to the spleen, which would be unusual with an infectious aetiology. Isolated splenic disease, which necessitates splenectomy was traditionally considered rare in the cat.[6] However, several recent feline case reports have described circumstances in which splenectomy was required.[7–9] In this case, it could be hypothesised that the changes seen in the spleen were suggestive of an early lymphoma, with the initial pathology result suggesting mantle cell lymphoma. Although this was not supported on subsequent immunohistochemistry or PARR analysis, splenic lymphoma is poorly described in the cat, with no series differentiating forms of feline splenic lymphoma and past B and T cells. It is therefore possible that a clonal population of neoplastic lymphocytes may have been present in the spleen, but which was not apparent histologically or on molecular testing due to the presence of a much larger population of non-neoplastic lymphocytes. Indeed in humans, hypercalcaemia has been documented in 'early' or 'premalignant lymphoma'.[4] Despite the availability of a far wider range of specific immunohistochemical and molecular assays than we have for veterinary species, identification of early lymphoma lesions (e.g., 'mantle cell lymphoma in situ') in people still remains challenging.[10] Hence, it is entirely possible that a histologically inapparent lymphoproliferative neoplasm may have been present in the spleen of this cat.

This case had a markedly elevated ionised calcium, which was refractory to standard therapy. In cats, the differential diagnoses for feline ionised hypercalcaemia include idiopathic disease, hyperparathyroidism, granulomatous disease, renal disease, vitamin D toxicity (25-hydroxycholcalciferol), neoplastic disease, osteolysis and rarely hypoadrenocorticism.[1] Investigations demonstrated low PTH and low PTHrP. 25-Hydroxycholcalciferol was not assessed, but the chronicity made toxin ingestion unlikely, and the diet was changed during the course of the disease. There were no lytic lesions on CT and prior to the angiography it was initially presumed that this cat had idiopathic hypercalcaemia, as no underlying cause was identified. The hypercalcaemia resolved once the spleen was removed, again suggesting that the lymphoid proliferations within the spleen was the cause of the hypercalcaemia. Hypercalcaemia has been reported in people with inflammatory and pre-malignant diseases,[3,4,11,12] but has not previously been reported in the cat. The hypercalcaemia is typically mediated by PTH or PTHrP (neither of which were abnormally raised in this case). However, in some cases, calcitriol or RANK-L-mediated hypercalcaemia occurs.[3] Recently, a case of hypercalcaemia in a dog has been linked to elevated calcitriol. In that case, histiocytic sarcoma was identified at postmortem examination.[13] Unfortunately, calcitriol assay was not available in this case.

Of particular interest are the infectious causes of hypercalcaemia, with both retroviral infection with HTLV-1 and bartonellosis having been associated with hypercalcaemia in people.[4,14] In this case, the cat tested negative for known feline retroviruses. While *Bartonella* infection is recognised in cats, and splenic sequestration has been suggested in some cases, prolonged courses of amoxicillin–clavulanate have demonstrated efficacy against this infection, which might argue against this as a potential cause in this case.[15]

Interestingly, there is a report of increased calcium uptake from the gastrointestinal tract in dogs receiving lactulose.[16] This was followed by the observation that eight of 119 cats in one retrospective study that were receiving lactulose, two cats demonstrated moderate/severe hypercalcaemia.[2] However, in that study, it was unclear when lactulose treatment had been implemented, as lactulose can be used to treat constipation in cats, which can be a symptom of hypercalcaemia, causality cannot be implied. In the case presented here, lactulose was administered prior to the onset of hypercalcaemia. However, the hypercalcaemia resolved within 2 weeks of the splenectomy after which normocalcaemia was maintained. The cat remained on lactulose throughout this time, with withdrawal of the medication occurring over 2 months after normocalcaemia had been achieved.

The case reported here was complicated by multiple abnormalities. Initially, the cat presented with hyperammonaemia, the differential diagnosis for which would have previously been limited to hepatic encephalopathy (PSS or severe hepatic disease), hypocobalaminaemia or in-built errors of metabolism.[17] These differentials were unlikely due to the

age of the cat, and were ruled out by blood/urinalysis. Seizure activity was considered, as this has been associated with increased ammonia in people and, recently, in cats.[18] However, the hyperammonaemia was present prior to clinically apparent seizure activity, and did not resolve despite control of the seizures. Hyperammonaemia has been reported in conjunction with certain chemotherapeutic medications.[19] However, the case reported here did not receive any such medications. In human beings, multiple myeloma has been associated with hyperammonaemia, with the proliferative cells producing ammonia in vivo.[20–22] This phenomenon has not been demonstrated in other cell lines. In this case, the aetiology of the hyperammonaemia is unknown and it is unclear why this abnormality took several weeks to resolve after the spleen was removed.

This cat also demonstrated an elevated cobalamin level. In humans, hypercobalaminaemia is associated with myeloproliferative, hepatic, renal, autoimmune and neoplastic diseases.[23] Similarly, high serum cobalamin has been reported in cats with inflammatory (particularly hepatic) and neoplastic diseases[24,25] and in a case of hyperammonaemia with increased methylmalonic aciduria.[26] Interestingly, in the study by Trehy et al., one of the 33 cats with hypercobalaminaemia was diagnosed with idiopathic hypercalcaemia.[25] In this case, the cause of the hypercobalaminaemia was not ascertained; interestingly, this has been a persistent feature despite resolution of all other abnormalities.

CONCLUSION

This case highlights the need for a better understanding of hypercalcaemia in cats. The diagnosis of idiopathic hypercalcaemia accounts for 11%–52% of cases. However, in such cases, neither calcitriol nor RANK-L testing is typically performed. Therefore, it is possible that other inflammatory, infectious or pre-neoplastic causes of hypercalcaemia are not being investigated.

AUTHOR CONTRIBUTIONS

Kerry E. Rolph was the primary clinician overseeing the case and main author. Tim Scase was the pathologist who interpreted the histopathology and edited the manuscript. Owen Davies provided follow-up to the case and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not specifically required for publication. Informed consent was obtained from the owner of the cat described in this work.

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ENDNOTE

* Langford Diagnostic Laboratories, Langford Vets, Langford, Bristol, UK.
† The laboratory was pre-informed of sample collection to allow for immediate assessment. Blood was transported on ice by veterinary ambulance directly to the laboratory (15 minutes) for ammonia analysis to be performed.
‡ b Biocontrol Veterinär labor partner, Labor für veterinärmedizinische Untersuchungen, Ingelheim, Germany.
§ In house assessment; Rapidpoint 500, Siemens.
‖ NationWide Laboratories, Cambridge, UK.
¶ Axiom Laboratories, Bristol, UK.
# Bridge Pathology, Bristol, UK.
** Veterinary Pathology Group (VPG) Molecular, Exeter, UK.

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