Severe Systemic Calciphylaxis in a Young Cat

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A 7-month-old female intact domestic shorthair/British Blue crossbreed cat was referred to the Queen Mother Hospital for Animals (QMHA) of the Royal Veterinary College for further investigation of progressive lethargy preceded by 48 hours of mixed bowel diarrhea, moderate pyrexia (39.9°C; 103.8°F), and unproductive retching. Laboratory tests performed at the primary practice identified marked hypercalcemia (serum total calcium concentration). Despite treatment with IV fluids and potentiated amoxicillin, the cat deteriorated clinically, prompting referral. On presentation to the QMHA, the cat was dull but responsive with poor body condition (3.5/9) and pyrexia (39.2°C; 102.6°F). Firm white lingual plaques were observed (Fig 1). Both kidneys were subjectively mildly enlarged. The remainder of the physical examination was unremarkable. With the exception of the cat's decreased mentation, neurologic examination was considered normal. No neurologic deficits suggesting a structural intracranial lesion were found at any point throughout the time the cat was hospitalized, but the level of obtundation would wax and wane. No association between the cat's mentation and the treatments administered was apparent.

Initial investigations confirmed marked total hypercalcemia (19.28 mg/dL; 4.82 mmol/L; reference interval [RI], 8.28–10.72 mg/dL) and ionized hypercalcemia (9.0 mg/dL; 2.25 mmol/L; RI, 4.52–5.32 mg/dL), with mild hyperphosphatemia (7.68 mg/dL; 2.48 mmol/L; RI, 2.85–6.69 mg/dL). Markedly increased serum CK activity was identified (21,322 U/L; RI, 52–506 U/L) increasing to 43,616 U/L upon repeated measurement after 3 days. Serum ALT activity was within normal limits. At the time of presentation, serum urea nitrogen concentration was moderately increased (49.0 mg/dL; 17.5 mmol/L; RI, 17.1–33.6 mg/dL), whereas serum creatinine concentration was within normal limits (1.36 mg/dL; 118 µmol/L; RI, 0.84–2.1 mg/dL).

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Abbreviations:

ALT	alanine aminotransferase
Ca × P	calcium × phosphate
CK	creatine kinase
DSH	domestic shorthair
H&E	hematoxylin and eosin
IRIS	international renal interest society
PTH	parathyroid hormone
PTHrP	PTH-related protein
QMHA	Queen Mother Hospital for Animals
RI	reference interval

Interpretation of complete blood cell count was consistent with a stress leukogram. Mild leukocytosis (26.2×10^9/L; RI, 5.5–19.5×10^9/L) with mild neutrophilia (23.8×10^9/L; RI, 2.5–12.5×10^9/L) and mild lymphopenia (0.58×10^9/L; RI, 1.5–7.0×10^9/L) were present. Urinalysis disclosed the presence of granular casts (10 per 81 high-power fields, 400×), but was otherwise unremarkable. Urine specific gravity was 1.015 (after IV fluid therapy).

Venous blood gas, electrolyte, and metabolite analyses were performed throughout hospitalization to monitor plasma creatinine, urea, and ionized calcium concentrations. Plasma ionized calcium concentration gradually decreased from 9.0 mg/dL to 7.44 mg/dL 24 hours after admission, whereas blood urea nitrogen and creatinine concentration increased to 142.6 mg/dL (50.9 mmol/L) and 3.0 mg/dL (268 µmol/L), respectively. The azotemia was believed to be at least partly prerenal, because it gradually resolved over the next 48 hours, with concurrent decreases in packed cell volume and total protein concentration (from 30% and 6.4 g/dL to 20% and 5.4 g/dL, respectively). During the first 3 days of hospitalization, treatment included IV fluid therapy (up to 8 mL/kg/h by the second day), furosemide[a] (0.5–1.0 mg/kg IV q6h), and salmon calcitonin[b] (4 IU/kg SC q8h), all of which were initiated on the first day of hospitalization. Furosemide probably contributed to dehydration and development of azotemia, supported by a 100 g (4.8%) decrease in body weight over the first 24 hours. Owing to persistent hypercalcemia despite treatment, IV pamidronate[c] infusion (1.75 mg/kg diluted in 16 mL 0.9% NaCl, infused at a rate of 4 mL/h) was administered on the third day of hospitalization, at which time salmon calcitonin was discontinued. These treatments failed to substantially alter the plasma ionized calcium concentration, but approximately 48 hours after initiating prednisolone[d] treatment (0.5 mg/kg PO q12h) on day 6 of hospitalization, plasma ionized calcium con-

Fig 1. Firm white lingual plaques observed at the time of presentation.

centration was within normal limits (4.76 mg/dL; 1.19 mmol/L). Plasma ionized calcium concentration subsequently increased to 6.04 mg/dL (1.51 mmol/L) and remained at that concentration for the remainder of hospitalization.

Thorough investigations did not identify an underlying cause for the hypercalcemia. Plasma parathyroid hormone (PTH)[e] concentration was 10 pg/ml (RI, <40 pg/mL; sample obtained at the time of ionized hypercalcemia), whereas plasma PTH-related protein (PTHrP)[f] concentration was equivocally increased (14.25 pg/mL; 1.5 pmol/L; RI, <9.5 pg/mL). Plasma PTHrP concentrations >20.9 pg/mL are considered suggestive of malignancy. Thoracic and abdominal imaging identified only nonspecific changes consistent with tissue mineralization, and neoplastic disease hence was considered unlikely. Thoracic radiography disclosed a diffuse bronchial pattern with mild bronchial mineralization. Abdominal radiography identified loss of serosal detail, consistent with lack of intra-abdominal fat; both kidneys appeared slightly enlarged. Abdominal ultrasound examination confirmed slight bilateral renomegaly (both kidneys measuring 4 cm in length), with hyperechoic speckled cortices and bilateral medullary rim sign. Bilateral pyelectasia (1–2 mm) was present, and attributed to IV fluid therapy. Fine-needle aspirates of the kidneys obtained under ultrasound guidance to investigate the possibility of renal lymphoma did not identify any lymphocytes or microorganisms. Because vitamin D toxicosis was a differential diagnosis for hypercalcemia in this patient (usually associated with mildly increased serum inorganic phosphorus concentration), plasma 25-hydroxyvitamin D concentration was measured, yielding a value of 22.8 ng/mL; 57 nmol/L (RI, 26.0–68.1 ng/mL). Granulomatous diseases are thought to cause hypercal-

cemia through synthesis of vitamin D analogs,[1] and could have explained the increased serum CK activity in this patient. However, a serum *Toxoplasma gondii* microagglutination test, a serum cryptococcal latex agglutination test, a feline coronavirus antibody titer, and a Baermann flotation for feline lungworm (*Aelurostrongylus* spp.) all were negative. Serum cortisol concentration was 6.8 μg/dL (188.0 nmol/L), probably ruling out glucocorticoid-deficient hypoadrenocorticism as a cause of the hypercalcemia. Looking for other explanations for the decreased and somewhat waxing and waning mentation, the possibility of a portosystemic vascular anomaly (PSVA) was explored. Plasma ammonia concentration was moderately increased (211 μg/dL; 124 μmol/L; RI, 0–102 μg/dL), whereas serum concentrations of pre- and postprandial bile acids were within normal limits, as were results of biochemical liver function tests in combination with an ultrasonographically normal appearance of the liver. These results suggested that a PSVA was highly unlikely. The hyperammonemia was considered unlikely to be of clinical relevance, because a direct association with the more clinically relevant findings in this patient (ie, marked hypercalcemia and widespread mineralization) was not apparent.

The cat's mentation did not change substantially despite transient normalization of the plasma ionized calcium concentration. In light of the poor quality of life and poor prognosis, the owner elected euthanasia. Postmortem examination confirmed calcification of the lungs, kidneys, major blood vessels, and skeletal muscles, the latter in combination with marked dystrophic lesions.

The most prominent features of the histopathologic examination were multifocal metastatic calcifications affecting multiple tissues, and multifocal degenerative myopathy (Fig 2). Several sections of skeletal muscle had multifocal myofiber atrophy, degeneration, and calcification with interstitial fibroplasia. Foci of ischemic necrosis affecting whole muscle fascicles occasionally were noted (eg, triceps brachii), demonstrating swelling and hypereosinophilia of affected myofibers. Multinucleated regenerative myofibers were interspersed with atrophic, degenerate, and calcified fibers. Lakes of calcified debris forming nodules at the lingual margins were present, as was multifocal gastric mucosal calcification. Radial cortical calcification, centered on tubular basement membranes, was demonstrated in the kidneys, providing an explanation for the granular casts. Multifocal basement membrane calcification of small airways and blood vessels also was observed, and the adrenal glands had focal calcification. Representative sections of the brain (cerebrum and medulla oblongata), spinal cord (with spinal nerve and dorsal root ganglion), and pituitary gland were microscopically normal, whereas parathyroid tissue was atrophic.

In light of the multiple muscle fiber abnormalities and markedly increased serum CK activity, a form of muscular dystrophy was considered as a differential diagnosis in this cat once a number of more common granulomatous diseases had been eliminated, but the
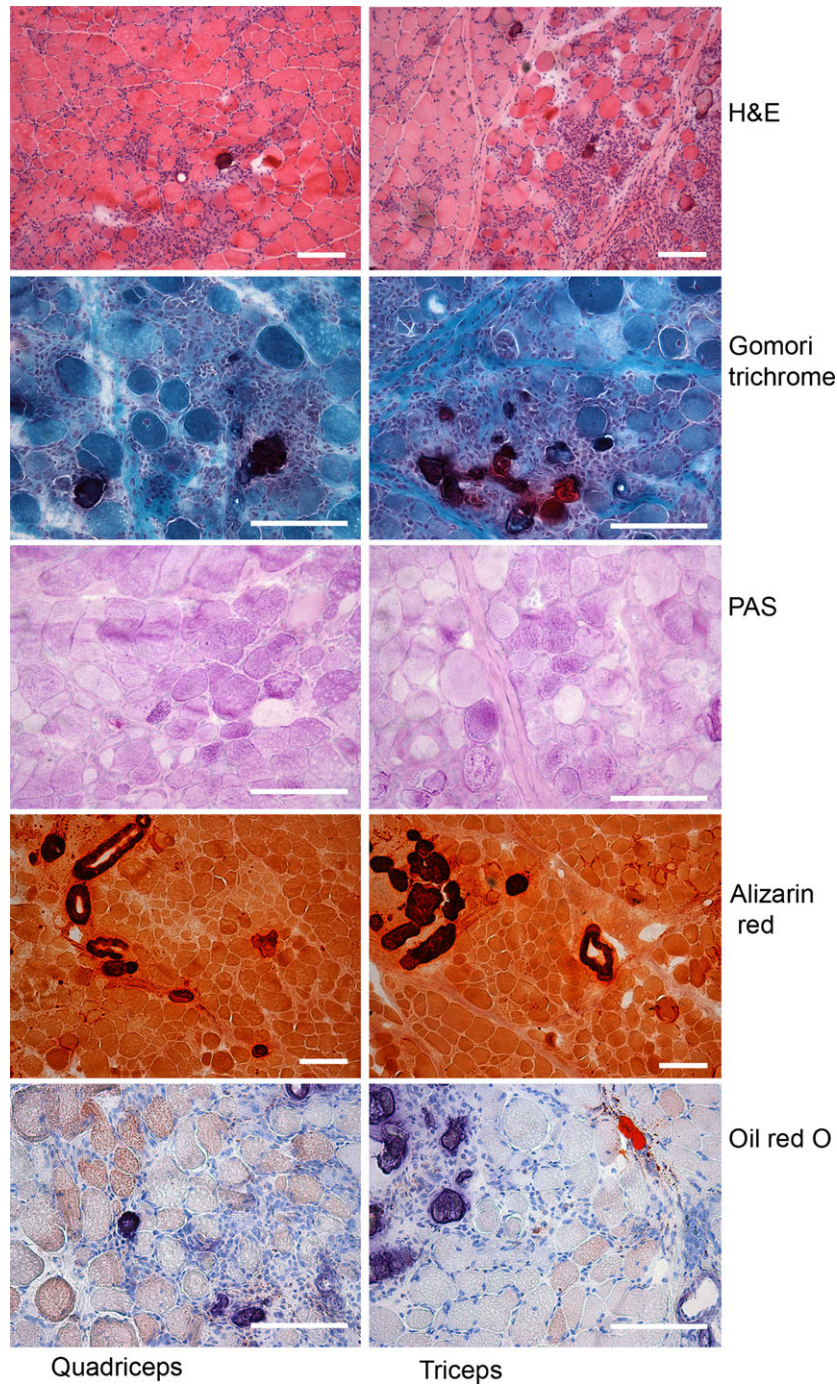
Fig 2. Staining panel performed on triceps and quadriceps biopsy fresh-frozen muscle sections. Note widespread dystrophic calcification and degeneration with islands of regenerating (basophilic) fibers, internalized nuclei, and infiltrating mononuclear cells (hematoxylin and eosin [H&E] and Gomori trichrome stains). Periodic acid Schiff stain identified small amounts of fine granular glycogen in most fibers, with some fibers devoid of glycogen. Alizarin red stain identified deposits of calcium salts in the walls of blood vessels, in the endomysium and within a few muscle fibers. Oil red O stain identified accumulation of lipid droplets (red specks) in the cytoplasm of some fibers. Scale bars = 100 μm.

hypercalcemia was considered unusual for a primary muscular dystrophy. Samples of quadriceps and triceps muscles were obtained immediately postmortem and snap-frozen in isopentane, cooled in liquid nitrogen. An extended staining panel conducted on 8 μm cryosections included hematoxylin and eosin, periodic acid Schiff, modified Gomori trichrome, oil red O, and Alizarin red (Fig 2). There were prominent dystrophic features within the triceps and quadriceps muscles, consisting of marked fiber size variation, numerous internalized nuclei, basophilic regenerating fibers, increased endomysial and perimysial connective tissue,

and large areas of infiltrating mononuclear cells (probably macrophages). The Alizarin red stain confirmed the presence of prominent accumulations of calcium in sarcoplasmic and extracellular regions, and there also was a marked accumulation of calcium deposits in the smooth muscle of blood vessels. Oil red O stain identified fine punctate lipid accumulation in many fibers.

Extensive diagnostic evaluation failed to disclose a definitive diagnosis for this cat. Neither of the described muscular dystrophies was considered to fit the clinical or histopathologic picture. The cat was female, hence X-linked dystrophin deficiency would be highly unlikely,[2] and the cat did not display the typical extensor contracture of the pelvic limbs or lipid accumulation in the muscle fibers seen with laminin α2 (merosin) deficiency,[2] nor the ventroflexed neck and dorsally protruding scapulae described in α-dystroglycan deficiency; moreover, the latter cases had normal CK activity.[3] Of the muscular dystrophies described in companion animals, β-sarcoglycan deficiency initially was considered a possibility in this cat. This condition has been associated with hypercalcemia in a domestic shorthair cat and a Boston Terrier, associated in both cases with markedly increased serum CK activity, but these patients had mild total hypercalcemia attributed to young age.[4,5] In light of the absence of muscle fiber hypertrophy, the marked hypercalcemia, and the widespread calcium deposition in other organs and blood vessels in our patient, we considered the dystrophic features of the muscle fibers likely to be an effect rather than a primary cause of the disease.

No underlying cause for this patient's hypercalcemia was identified, rendering idiopathic hypercalcemia our presumptive diagnosis. Although serum PTHrP concentration was mildly increased, no evidence of neoplasia was found on postmortem examination. Despite the detectable plasma PTH concentration, primary hyperparathyroidism was ruled out on the basis of the atrophic parathyroid glands. Furthermore, this is a rare condition in cats, usually presenting in older animals and associated with a low-normal to decreased serum phosphate concentration.[6] Although increased concentrations of plasma ionized calcium, PTH, and phosphate would be expected in so-called 'tertiary hyperparathyroidism', this condition has only been described infrequently in cats with advanced renal disease (IRIS stages 3–4), after a period of renal secondary hyperparathyroidism.[7] This was not consistent with the mild, transient azotemia in this patient, and would have resulted in hyperplasia of the parathyroid glands.

Although idiopathic hypercalcemia is relatively common in cats, reportedly accounting for an increasing proportion of hypercalcemia in this species,[8] severe metastatic calcification has hitherto not been described in these patients. Serum phosphate concentration was above the RI in this patient, resulting in a markedly increased Ca × P product. Young animals normally have higher calcium or phosphate concentrations or both than adults and are thought to be more resistant to tissue mineralization.[9] However, the magnitude of

the electrolyte derangements in this patient accounted for the severe, widespread mineralization.

Calciphylaxis is a term that was first used by Seyle to describe a 'systemic hypersensitivity' resulting in systemic calcification in animals that were sensitized by so-called 'calcifiers' (eg, vitamin D analogs, PTH) and subsequently exposed to a 'challenger' (eg, iron, aluminum, trauma).[10] In humans, a similar syndrome of calciphylaxis or systemic calcinosis also is called calcific uremic arteriolopathy, and is a rare condition usually seen in patients with end-stage renal disease and in renal transplant patients.[11,12] Although incompletely understood, consequences of their disease such as hyperphosphatemia and tertiary hyperparathyroidism are thought to play a role.[11,12] In companion animals, systemic calcification has been described in patients with vitamin D intoxication resulting in hypercalcemia and hyperphosphatemia, as well as renal disease.[13–16] The calcification in these human and veterinary patients has occurred primarily within the intima of blood vessel walls, resulting in ischemia and necrosis with subsequent mineralization.[11–15] In our patient, subintimal calcification was noted in larger blood vessels as well as in blood vessels in the musculature, including the myocardium, with associated ischemia, necrosis, and calcification. However, calcium deposits also were demonstrated within the myoplasma (best visualized with the Alizarin red stain, Fig 2). This pathology is unusual in humans, and when present usually is preceded by calcification of the skin.[12,17] To our knowledge, extensive calcification of the striated musculature has not been demonstrated previously in either cats or dogs without preexisting muscular disease,[13–15,18,19] but a recent case series described systemic calcification in 5 horses, all of which exhibited muscle calcification and increased serum CK activities.[20] The reason for calcification in these patients was unclear, but the authors speculated that they were 'sensitized' by an increased Ca × P product (2 horses) or hyperphosphatemia (5 horses), and subsequently challenged by steroids, plasma administration, trauma, an inflammatory condition, or some combination of these factors, resulting in systemic calcification. Interestingly, all of these horses had decreased (2 horses) or normal (3 horses) calcium concentrations, and only 2 had an increased Ca × P product. A recent report described idiopathic calciphylaxis in a 10-week-old male domestic shorthair kitten,[21] but this kitten differed from our patient by predominantly presenting for severe cutaneous lesions and experiencing full recovery with symptomatic treatment. Furthermore, apart from assumed age-related hyperphosphatemia, the kitten's laboratory test results were unremarkable, including a normal Ca × P product. The cutaneous calcification was hypothesized to represent an inherited disorder. Unlike our patient, this kitten did not have any apparent reason for generalized mineralization, possibly explaining why the calcification was limited to the skin. Our patient suffered from systemic calcification involving muscle and visceral organs, presumptively a consequence of the markedly increased

Ca × P product. The potentially deleterious consequences of an increased Ca × P product emphasize the importance of monitoring the Ca × P product in hypercalcemic patients, and suggest that every effort should be made to decrease it (and thereby probably the risk of mineralization) as soon as possible.

This report describes, to our knowledge, the first documentation of severe systemic calciphylaxis with hypercalcemia in a cat. On the basis of the clinical presentation and thorough ante- and postmortem investigations, we conclude that the markedly increased Ca × P product in this patient accounted for the mineralization, with the extensive muscle fiber calcification explaining the markedly increased serum CK activity. We consider the patient's decreased mentation to be a result of the systemic effects of the severe tissue mineralization, which did not resolve within a matter of days[15,22] despite transient normocalcemia. Pain is one of the initial signs of calciphylaxis in humans,[23] and the cat may have responded to painful sensation with decreased mentation, although the cat did not appear painful when handled. The hypercalcemia itself also may have contributed to this patient's decreased mentation. Human patients with hypercalcemia related to primary hyperparathyroidism can present with headaches, fatigue, nausea, and mental disturbances, including coma.[24] These signs have been found to correlate with the degree of hypercalcemia rather than plasma PTH concentration, with clinical improvement corresponding to decreasing calcium concentration despite persistently high PTH concentration.[24] The lack of clinical improvement in our patient at the time of normocalcemia, however, does not support hypercalcemia as the sole cause of obtundation. Hyperammonemia contributing to the patient's decreased mentation was considered unlikely, but could not be eliminated. Because mammalian muscle produces ammonia,[25] muscle necrosis may have caused the hyperammonemia in this patient.

Footnotes

[a] Furosemide monoethanolamine (Dimazon, injectable, 5% w/v Furosemide monoethanolamine; per 1 mL: 50 mg Furosemide monoethanolamine, 15 mg benzyl alcohol, 1 mg Disodium Edetate Dihydrate, and 1.8 mg sodium Sulphite Anhydrous), Intervet UK Ltd, Walton Manor, Milton Keynes, Bucks, MK7 7AJ, UK

[b] Calcitonin Salmon (Miacalcic, injectable, 100 IU/mL), Sandoz Pharmaceuticals, Frimley Business Park, Camberley, Surrey, GU16 7SR, UK

[c] Pamidronate disodium pentahydrate (Aredia, 15 mg/5 mL), Ciba Laboratories, Frimley Business Park, Camberley, Surrey, GU16 7SR, UK

[d] Prednisolone (Prednicare tablets, 1 mg), Animal Care ltd, York, YO19 5RU, UK

[e] Enzyme-linked immunosorbent assay, IDS limited, Cambridge Specialist Laboratories, UK. Canine PTH assay validated for felines by parallelism (unpublished results, personal communication)

[f] Radioimmunoassay, Beckman Coulter, Cambridge Specialist Laboratories, UK. Human PTHrP assay validated for felines by the laboratory (unpublished results, personal communication)

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