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Case Report

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Non-islet-cell tumour hypoglycaemia in a cat with hepatocellular carcinoma

Alexandra Guillen[1], Lorenzo Ressel[2], Riccardo Finotello[1], Alexander J German[1], Alistair Freeman[1] and Laura Blackwood[1]

Abstract

Case summary An 11-year-old male neutered domestic shorthair cat presented with behavioural changes. Physical examination revealed bradycardia and a cranial abdominal mass. The cat was persistently hypoglycaemic (1.2 mmol/l; reference interval [RI] 3.5–5.5 mmol/l) with decreased fructosamine concentration suggesting chronic hypoglycaemia, and decreased insulin concentration excluding insulinoma. Alanine aminotransferase activity was markedly increased (1219.31 U/l; RI 15–60 U/l). On staging CT a large, multilobulated hepatic mass was identified, with no evidence of metastatic disease. After surgical removal serum glucose concentration and heart rate quickly returned to within the RIs. Histopathology was consistent with a solid-to-trabecular, well-differentiated, hepatocellular carcinoma. There was no recurrence of signs or mass during 8 months of follow-up, and the cat was still alive 20 months after surgery.

Relevance and novel information Non-islet-cell tumour hypoglycaemia (NICTH) is a rare but life-threatening paraneoplastic syndrome. In humans, hepatocellular carcinoma is the most common epithelial tumour causing NICTH, but these are uncommon in cats, and associated paraneoplastic hypoglycaemia has not been reported. Possible mechanisms include aberrant secretion of big insulin growth factor 2; however, this could not be confirmed. NICTH should be considered in the differential diagnosis of cats with persistent hypoglycaemia.

Keywords: IGF-2; hypoglycaemia; insulin growth factor 2; hepatocellular carcinoma; HCC; paraneoplastic

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Case description

An 11-year-old male neutered domestic shorthair cat presented with a 3 month history of intermittent behavioural changes (excitability, pacing and disorientation). No seizures or collapsing episodes had been observed. On presentation the cat was bright, alert and responsive, with a body condition score of 4/9 (weight 3.9 kg). General physical examination revealed moderate bradycardia (heart rate 80–100 beats per min), regular cardiac rhythm, synchronic femoral pulses and a firm, non-painful mass in the cranial abdomen. Pupillary light reflex was bilaterally reduced, but the cat had no problems navigating around the consultation room when allowed to.

Haematology was within the reference intervals (RIs). Serum biochemistry revealed severe hypoglycaemia (1.2 mmol/l; RI 3.5–5.5 mmol/l), markedly increased alanine aminotransferase (ALT) activity (1219 U/l; RI 15–60 U/l) and mildly increased alkaline phosphatase activity (90 U/l; RI 0–40 U/l). Coagulation times, bilirubin and pre-prandial bile acids were within the RIs, as were total thyroxine and basal cortisol

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concentrations. Feline immunodeficiency virus and feline leukaemia virus SNAP tests (IDEXX Laboratories) were negative. Electrocardiography revealed sinus bradycardia and systolic blood pressure (Doppler device) was 140 mmHg. Measurement of fructosamine concentration confirmed chronic hypoglycaemia and insulin concentration (immunoradiometric assay; Nationwide Specialists Laboratories, Cambridge, UK) was not consistent with insulinoma. Insulin autoantibody serology was negative, essentially excluding immune-mediated disease as the cause of hypoglycaemia. Serum insulin growth factor 1 (IGF-1; radioimmunoassay [Nationwide Specialists Laboratories, Cambridge, UK]) was within the RI (Table 1).

CT of the head, thorax and abdomen revealed a 15 cm maximum diameter, multilobular cystic mass arising from the caudal left liver lobe (Figure 1). The spleen was diffusely heterogeneous and slightly enlarged. Ultrasound-guided fine-needle aspirates of the mass revealed well-differentiated, vacuolated hepatocytes. Fine-needle aspirates from the spleen showed no cytological abnormalities. Histopathological evaluation of a needle core biopsy of the liver mass suggested either primary hepatocellular carcinoma (HCC) or hepatoma.

Table 1 Additional tests

	Day 1	Day 24	Day 124	Reference interval
Basal cortisol (nmol/l)	180	–	–	50–250
Total thyroxine (nmol/l)	29.9	–	–	5–44
FIV/FeLV SNAP test	Negative	–	–	
Insulin (µIU/ml)	<3	–	–	3.7–11.4
Fructosamine (µmol/l)	160	207	259	<300
IGF-1 (ng/ml)	295	586	–	50–1000
Insulin autoantibodies (%)	5	–	–	<20

FIV = feline immunodeficiency virus; FeLV = feline leukaemia virus; IGF = insulin growth factor

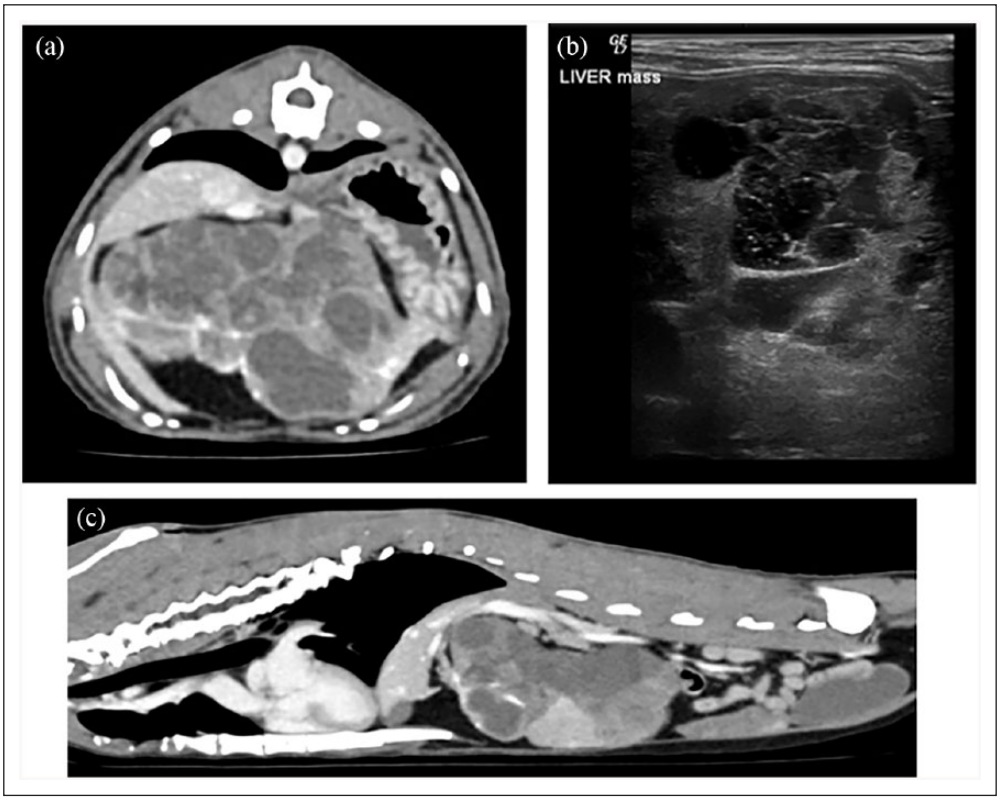


Figure 1 (a) Transversal image of the CT scan showing a large, multilobulated, hepatic mass. (b) Ultrasonographic appearance of the liver tumour. (c) Sagittal image of the thorax and abdomen showing heterogeneous contrast enhancement of the liver

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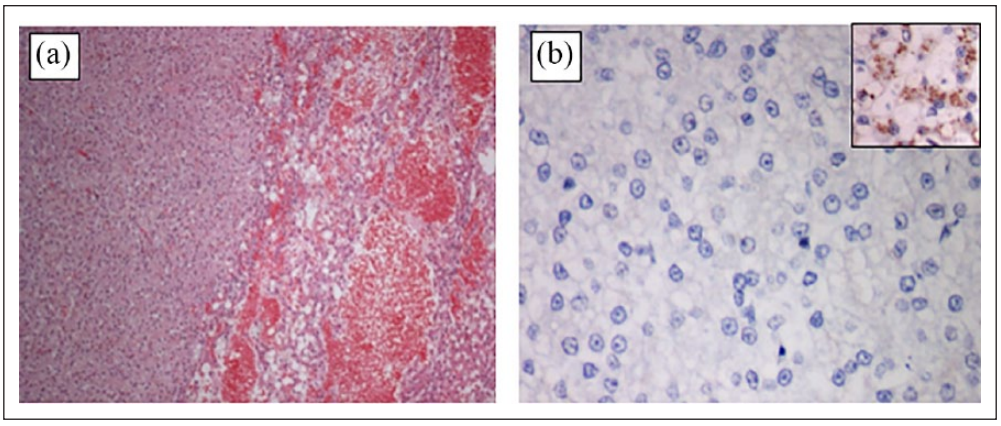


Figure 2 (a) Micrograph of the hepatocellular carcinoma on the left, with normal congested hepatic parenchyma on the right. Haematoxylin and eosin, × 200. (b) Micrograph showing the negative immunostaining for insulin growth factor 2 (IGF-2). Inset: positive IGF-2 staining in the normal liver

The cat was hospitalised for 48 h awaiting surgical excision of the liver mass, and hypoglycaemia persisted despite administration of glucose, dextrose and prednisolone. The left lateral liver lobe and associated mass were excised en bloc using an Endo GIA stapler with a 2.5 mm vascular cartridge placed across the lobe base. Abdominal exploration showed no gross evidence of metastatic disease.

Histopathological examination of the mass revealed well-differentiated but neoplastic hepatocytes with mild-to-moderate anisokaryosis and anisocytosis (mitotic index 2 per 10 high-power fields), consistent with a solid to trabecular, well-differentiated hepatocellular carcinoma. IGF-2 immunohistochemistry on sections from formalin-fixed, paraffin-embedded liver biopsies using an IGF-2 antibody (1:200; ab9574 [Abcam]), and feline colonic tissue as a positive control, revealed scattered positive staining in normal hepatocytes but not in neoplastic cells (Figure 2).

Serum glucose concentration and heart rate normalised within 2 h of tumour removal. Twenty-four days after surgery the patient was normoglycaemic, and serum ALT was practically normal (68.84 U/l; RI 15–60 U/l). At follow-up 4 and 8 months after surgery no hypoglycaemic events or abnormal behaviour were reported. On both occasions, ultrasonographic examination revealed no tumour recurrence. Maintenance treatment with toceranib phosphate (Palladia; Zoetis) was discussed with the owner (based on the evidence of the use of the tyrosine kinase inhibitor sunitinib in humans with HCC[1] and the poorly understood behaviour of this tumour in cats) but declined. The patient was still alive 20 months after diagnosis.

Discussion

In non-islet-cell tumour hypoglycaemia (NICTH), IGFs, which have insulinomimetic effects, are secreted by the tumour, resulting in NICTH.[2–7] Mutations in tumour cells cause aberrant secretion of the prohormone big IGF-2,[8] which promotes cell growth, suppresses pituitary secretion of growth hormone and suppresses endogenous secretion of IGF-I and insulin by the liver.[2–7] In humans, NICTH is most commonly due to an HCC,[7,9] and diagnosis is based on sustained low blood growth hormone and IGF-1 concentrations, increased total IGF-2 concentration and a high IGF-2:IGF-1 ratio.[5,10] However, the mechanism of increased IGF-2 remains poorly understood and overproduction is also seen in chronic hepatitis and hepatic regeneration.[11] Moreover, some patients with NICTH have normal-to-reduced circulating total IGF-2 concentrations, suggesting that genetic aberrations in the synthesis of this hormone predominantly produce big IGF-2 instead.[9] Thus, diagnosis is often confirmed by resolution of hypoglycaemia after surgical removal of the tumour, as in this case.[8,12]

NICTH is associated with several tumours in dogs, including leiomyoma, leiomyosarcoma, mammary carcinoma, renal adenocarcinoma, renal lymphoma and gastrointestinal stromal tumours.[12–16] There is also a case report of a cat with a hepatoma and hypoglycaemia.[17] Only two case reports in the veterinary literature describe paraneoplastic hypoglycaemia with an HCC, in a dog and a horse.[13,18] To our knowledge, this is the first report of HCC-associated NICTH in a cat.

Full characterisation of NICTH was difficult in this case. IGF-1 can be measured in cats, but IGF-2 assays are not currently available. In this cat, there was circumstantial evidence for an IGF-2 or IGF-2-like mechanism as the IGF-1 concentration was in the lower third of the RI, despite decreased serum insulin concentration. This could be due to reduced production of IGF-1 by the diseased liver or reduced growth hormone stimulation.[11] When assaying IGF-1, however, insulin-like growth factor binding proteins may cause interference leading to

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either false-low or false-high concentrations.[19] Also, the RI for this test is not well established.[19] Further, the IGF-1 concentration was almost double the preoperative concentration, 24 days after surgery (Table 1); together with the decreased insulin concentration, this could reflect removal of an IGF-2-producing tumour.

Immunohistochemistry was performed with an IGF-2 antibody previously validated in dogs.[2] The presence of positive staining in non-neoplastic cells was expected as IGF-2 is expressed in non-neoplastic hepatocytes. The lack of obvious overexpression of IGF-2 in neoplastic cells could be due to lack of complete antigen specificity for big IGF-2, or lack of antigen specificity due to genetic mutations in the tumour, resulting in production of aberrant forms of the protein. This is not an unusual finding in human HCCs, with overexpression being reported in only 15% of HCCs in one study.[6,20]

Hypoglycaemia resulting from an increased consumption of glucose within the tumour could not be fully excluded but was considered unlikely.

The clinical signs reported in this case are unusual. The neurological signs (excitability, pacing and disorientation) were attributed to neuroglycopenia. The brain has limited glycogen reserves and has high basal glucose requirements: in humans with hypoglycaemia, anxiety, irritability, dysphoria and confusion are common.[5,8] Similarly, the bradycardia was likely the result of sustained hypoglycaemia causing alterations in the physiology of myocardial tissue, as reduced extracellular glucose concentration inhibits function of the repolarising K^+ channel leading to action potential prolongation.[21] The bradycardia resolved postoperatively as glucose normalised.

The treatment of choice in humans with NICTH is surgical excision of the neoplasm.[7,8] Patients can also benefit from a high carbohydrate diet, including low glycaemic index foods and infused dextrose.[5] For inoperable tumours, recombinant growth hormone, continuous glucagon infusions, diazoxide and systemic chemotherapy have also been used to control paraneoplastic hypoglycaemia.[7,22,23]

The long-term prognosis for the massive form of HCC is fair to good in cats, although recurrence is relatively common.[24–26] Reported median survival time in 19 cats was 1.4 years, with cats treated surgically achieving median survival times of 2.4 years.[26] The current case also confirms a proportion of cats with HCC can enjoy long disease-free intervals.

Conclusions

This report describes an uncommon presentation of paraneoplastic hypoglycaemia in a cat with an HCC, with successful management and follow-up. Although this is considered a rare paraneoplastic syndrome, development of validated laboratory tests to confirm the diagnosis in cats with suspected IGF-2 overexpression are warranted.

Conflict of interest AJG is an employee of the University of Liverpool, but his post is financially supported by Royal Canin. AJG has also received financial remuneration for providing educational material, speaking at conferences and consultancy work from this company; all such remuneration has been for projects unrelated to the work reported in this manuscript.

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Ethical approval This work involved the use of client-owned animal(s) only, and followed established internationally recognised high standards ('best practice') of individual veterinary clinical patient care. Ethical Approval from a committee was not therefore needed.

Informed consent Informed written consent was obtained from the owner or legal guardian of all animal(s) described in this work for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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