



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

Authors: Guillen, Alexandra, Ressel, Lorenzo, Finotello, Riccardo, German, Alexander J, Freeman, Alistair, et al.

Source: Journal of Feline Medicine and Surgery Open Reports, 5(1)

Published By: SAGE Publishing

URL: <https://doi.org/10.1177/2055116919856129>

---

BioOne Complete ([complete.BioOne.org](https://complete.BioOne.org)) is a full-text database of 200 subscribed and open-access titles in the biological, ecological, and environmental sciences published by nonprofit societies, associations, museums, institutions, and presses.

Your use of this PDF, the BioOne Complete website, and all posted and associated content indicates your acceptance of BioOne's Terms of Use, available at [www.bioone.org/terms-of-use](https://www.bioone.org/terms-of-use).

Usage of BioOne Complete content is strictly limited to personal, educational, and non - commercial use. Commercial inquiries or rights and permissions requests should be directed to the individual publisher as copyright holder.

---

BioOne sees sustainable scholarly publishing as an inherently collaborative enterprise connecting authors, nonprofit publishers, academic institutions, research libraries, and research funders in the common goal of maximizing access to critical research.



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

Alexandra Guillen<sup>1</sup>, Lorenzo Ressel<sup>2</sup>, Riccardo Finotello<sup>1</sup>, Alexander J German<sup>1</sup>, Alistair Freeman<sup>1</sup> and Laura Blackwood<sup>1</sup>

*Journal of Feline Medicine and Surgery Open Reports*  
1–5

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/2055116919856129

journals.sagepub.com/home/jfmsopenreports

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS Open Reports*



## 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

**Accepted:** 21 May 2019

## 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

<sup>1</sup>Department of Small Animal Clinical Science, Institute of Veterinary Science, University of Liverpool, Neston, UK

<sup>2</sup>Department of Veterinary Pathology and Public Health, Institute of Veterinary Sciences, University of Liverpool, Neston, UK

### Corresponding author:

Alexandra Guillen DVM, MRCVS, Small Animal Teaching Hospital, University of Liverpool, Chester High Road, Neston CH64 7TE, UK

Email: a.guillen@liverpool.ac.uk



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

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

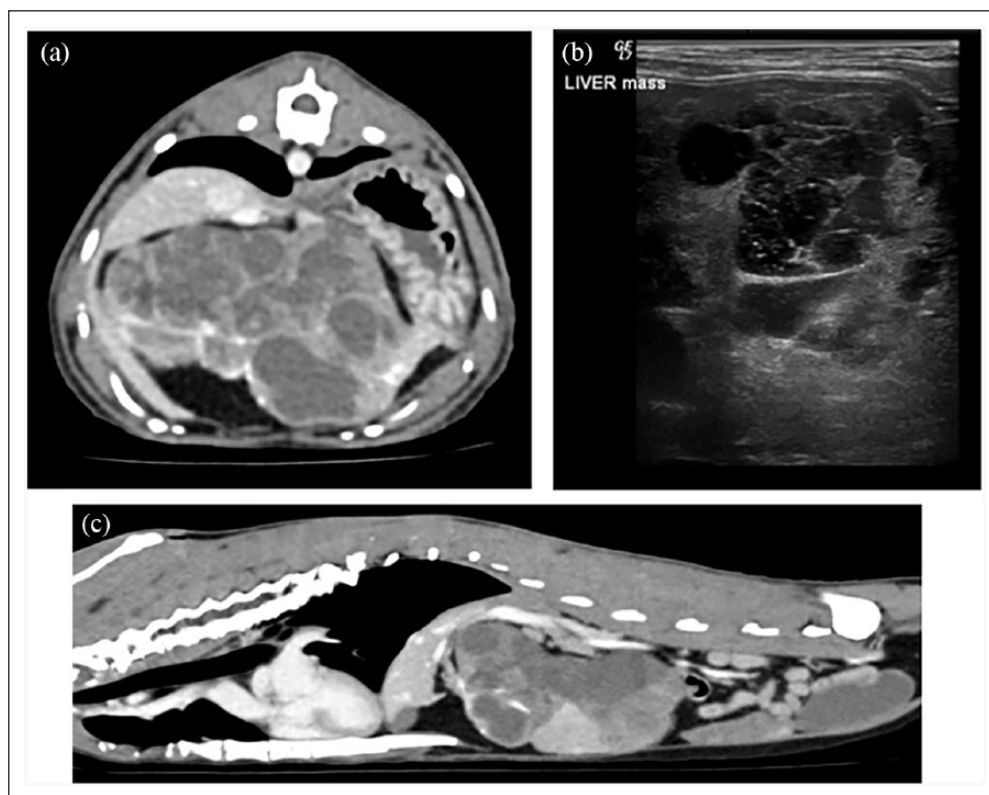
[Nationwide Specialists Laboratories, Cambridge, UK]) was within the RI (Table 1).

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.

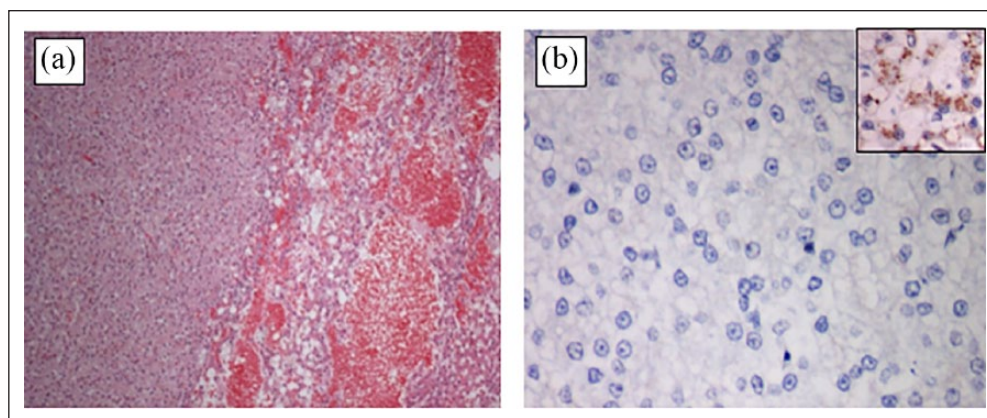
**Table 1** Additional tests

|                             | 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 ( $\mu$ IU/ml)      | <3       | –      | –       | 3.7–11.4           |
| Fructosamine ( $\mu$ mol/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



**Figure 2** (a) Micrograph of the hepatocellular carcinoma on the left, with normal congested hepatic parenchyma on the right. Haematoxylin and eosin,  $\times 200$ . (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<sup>1</sup> 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.<sup>2–7</sup> Mutations in tumour cells cause aberrant secretion of the prohormone big IGF-2,<sup>8</sup> which promotes cell growth, suppresses pituitary secretion of growth hormone and suppresses endogenous secretion of IGF-1 and insulin by the liver.<sup>2–7</sup> In humans, NICTH is most commonly due to an HCC,<sup>7,9</sup> 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.<sup>5,10</sup> However, the mechanism of increased IGF-2 remains poorly understood and overproduction is also seen in chronic hepatitis and hepatic regeneration.<sup>11</sup> 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.<sup>9</sup> Thus, diagnosis is often confirmed by resolution of hypoglycaemia after surgical removal of the tumour, as in this case.<sup>8,12</sup>

NICTH is associated with several tumours in dogs, including leiomyoma, leiomyosarcoma, mammary carcinoma, renal adenocarcinoma, renal lymphoma and gastrointestinal stromal tumours.<sup>12–16</sup> There is also a case report of a cat with a hepatoma and hypoglycaemia.<sup>17</sup> Only two case reports in the veterinary literature describe paraneoplastic hypoglycaemia with an HCC, in a dog and a horse.<sup>13,18</sup> 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.<sup>11</sup> When assaying IGF-1, however, insulin-like growth factor binding proteins may cause interference leading to

either false-low or false-high concentrations.<sup>19</sup> Also, the RI for this test is not well established.<sup>19</sup> 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.<sup>2</sup> 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.<sup>6,20</sup>

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.<sup>5,8</sup> 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<sup>+</sup> channel leading to action potential prolongation.<sup>21</sup> The bradycardia resolved postoperatively as glucose normalised.

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

The long-term prognosis for the massive form of HCC is fair to good in cats, although recurrence is relatively common.<sup>24–26</sup> Reported median survival time in 19 cats was 1.4 years, with cats treated surgically achieving median survival times of 2.4 years.<sup>26</sup> 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.

**Funding** The authors received no financial support for the research, authorship, and/or publication of this article.

**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.

## References

- 1 Raoul JL, Kudo M and Finn RS. **Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond.** *Cancer Treat Rev* 2018; 68: 16–24
- 2 Finotello R, Ressel L, Arvigo M, et al. **Canine pancreatic islet cell tumours secreting insulin-like growth factor type 2: a rare entity.** *Vet Comp Oncol* 2016; 14: 170–180.
- 3 Van den Berg SAA and Krol CG. **Pro-IGF2-induced hypoglycaemia associated with hepatocellular carcinoma.** *Endocrinol Diabetes Metab* 2017; 16: 17-0004.
- 4 Daughaday WH. **The pathophysiology of IGF-II hypersecretion in non-islet cell tumor hypoglycaemia.** *Diabetes Rev* 1995; 3: 62–72.
- 5 Han G, Zhang Z and Shen X. **Doerge-Potter syndrome: a review of the literature including a new case report.** *Medicine (Baltimore)* 2017; 96: e7417.
- 6 Martinez-Quetglas I, Pinyol R, Dauch D, et al. **IGF2 is up-regulated by epigenetic mechanisms in hepatocellular carcinomas and is an actionable oncogene product in experimental models.** *Gastroenterology* 2016; 151: 1192–1205.
- 7 Bodnar TW, Acevedo MJ and Pietropaolo M. **Management of non-islet-cell tumor hypoglycemia: a clinical review.** *J Clin Endocrinol Metab* 2014; 99: 713–722.
- 8 de Groot JW, Rikhof B, van Doorn J, et al. **Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases.** *Endocr Relat Cancer.* 2007; 14: 979–993.
- 9 Jeng JE, Chuang LY, Chuang WL, et al. **Insulin-like growth factor II in hepatocellular carcinoma.** *Biomark Med* 2007; 1: 261–271.
- 10 Frystyk J, Skjaerbaek C, Zapf J, et al. **Increased levels of circulating free insulin-like growth factors in patients with non-islet cell tumour hypoglycaemia.** *Diabetologia* 1998; 41: 589–594.

- 11 Adamek A and Kasprzak A. **Insulin-like growth factor (IGF) system in liver diseases.** *Int J Mol Sci* 2018; 19: E1308. DOI: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5983723/>.
- 12 Boari A, Barreca A, Bestetti GE, et al. **Hypoglycemia in a dog with a leiomyoma of the gastric wall producing an insulin-like growth factor II-like peptide.** *Eur J Endocrinol* 1995; 132: 744–750.
- 13 Zini E, Glaus TM, Minuto F, et al. **Paraneoplastic hypoglycemia due to an insulin-like growth factor type-II secreting hepatocellular carcinoma in a dog.** *J Vet Intern Med* 2007; 21: 193–195.
- 14 Leifer CE, Peterson ME, Matus RE, et al. **Hypoglycemia associated with nonislet cell tumor in 13 dogs.** *J Am Vet Med Assoc* 1985; 186: 53–55.
- 15 Snead EC. **A case of bilateral renal lymphosarcoma with secondary polycythaemia and paraneoplastic syndromes of hypoglycaemia and uveitis in an English Springer Spaniel.** *Vet Comp Oncol* 2005; 3: 139–144.
- 16 Rossi G, Errico G, Perez P, et al. **Paraneoplastic hypoglycemia in a diabetic dog with an insulin growth factor-2-producing mammary carcinoma.** *Vet Clin Pathol* 2010; 39: 480–484.
- 17 Thompson JC, Hickson PC, Johnstone AC, et al. **Observations on hypoglycaemia associated with a hepatoma in a cat.** *N Z Vet J* 1995; 43: 186–189.
- 18 Roby KA, Beech J, Bloom JC, et al. **Hepatocellular carcinoma associated with erythrocytosis and hypoglycemia in a yearling filly.** *J Am Vet Med Assoc* 1990; 196: 465–467.
- 19 Strage EM, Theodorsson E, Ström Holst B, et al. **Insulin-like growth factor I in cats: validation of an enzyme-linked immunosorbent assay and determination of biologic variation.** *Vet Clin Pathol* 2015; 44: 542–551.
- 20 Maake C and Reinecke M. **Immunohistochemical localization of insulin-like growth factor 1 and 2 in the endocrine pancreas of rat, dog, and man, and their coexistence with classical islet hormones.** *Cell Tissue Res* 1993; 273: 249–259.
- 21 Nordin C. **The proarrhythmic effect of hypoglycemia: evidence for increased risk from ischemia and bradycardia.** *Acta Diabetol* 2014; 51: 5–14.
- 22 Huang JS and Chang PH. **Refractory hypoglycemia controlled by systemic chemotherapy with advanced hepatocellular carcinoma: a case report.** *Oncol Lett* 2016; 11: 898–900.
- 23 Kampitak T. **Successful treatment of non-islet cell tumor hypoglycemia in hepatocellular carcinoma with doxorubicin.** *Cancer Chemother Pharmacol* 2008; 62: 929–930.
- 24 Liptak JM. **Hepatobiliary tumors.** In: Withrow SJ and MacEwen EG (eds). *Small animal clinical oncology*. 4th ed. Philadelphia, PA: WB Saunders, 2007.
- 25 Post G and Patnaik AK. **Nonhematopoietic hepatic neoplasms in cats: 21 cases (1983–88).** *J Am Vet Med Assoc* 1992; 7: 1080–1082.
- 26 Goussev SA, Center SA, Randolph JF, et al. **Clinical characteristics of hepatocellular carcinoma in 19 cats from a single institution (1980–2013).** *J Am Anim Hosp Assoc* 2016; 52: 36–41.