

Insulinoma in a cat

A 14-year-old domestic shorthair cat was presented with hypoglycaemia and seizures of several weeks duration. Bloodwork revealed hypoglycaemia (1.83 mmol/l; reference range 4.22-8.05 mmol/l) with concurrent normal insulin levels (171 pmol/l; reference range 72-583 pmol/l). An insulinoma was suspected and medical and dietary management were attempted with minimal success. An exploratory laparotomy was performed and a single, well-defined mass was found within the left lobe of the pancreas. The mass was removed and histologically classified as an islet cell carcinoma, consistent with an insulinoma. The cat had an episode of presumed postoperative pancreatitis, but recovered with appropriate treatment. The cat has had no clinical signs of recurrence of greater than 32 months postsurgery. There are only four cases of insulinoma in cats reported in the literature. All prior insulinomas reported were in older cats and were malignant in character, which is similar to the reports in the dog. This case is unique because of the apparent lack of local recurrence and development of metastatic disease, leading to the prolonged survival.

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INTRODUCTION

Insulinomas are functional beta-cell tumours arising from pancreatic islet cells. Neoplastic beta cells originate from amine precursor uptake and decarboxylation cells and produce moderate to excessive levels of neuroendocrine hormones, which can then be released into circulation (Ehrhart and others 1996). With insulinomas, there is an abnormal release of insulin. This drives the blood glucose concentration below normal, causing the clinical signs commonly associated with these tumours.

Insulinomas are uncommon in the dog and ferret and rare in the cat (Elie and Zerbe 1995). In the dog and cat, the most common signs seen are seizures, weakness, collapse, muscle twitching or other bizarre behaviour. Depression, collapse, splenomegaly, ptyalism and vomiting are more commonly reported clinical signs in ferrets (Caplan and others 1996, Weiss and others 1998).

Suspicion of an insulinoma should be raised when an adult animal is presented

with suggestive clinical signs as well as persistent hypoglycaemia (blood glucose <3.33 mmol/l). Further testing should include insulin concentration, which is typically normal to high despite hypoglycaemia. Abdominal radiographs and ultrasound have been minimally useful in the diagnosis of insulinoma; however, they may identify possible metastatic disease (Feldman and Nelson 2004). Medical therapy, including glucocorticoid therapy, diazoxide, somatostatin and frequent feedings have had limited use and efficacy in the cat. In the dog and cat, surgery is the treatment of choice (Tobin and others 1999), but owners should be informed that insulinomas are typically malignant and the long-term prognosis is poor.

CASE HISTORY

A 14-year-old, neutered, male domestic shorthair cat was presented with a several-week history of hypoglycaemia and seizure-like episodes. Physical examination by the referring veterinarian was within normal limits. Blood glucose at that time was 3.22 mmol/l. The blood glucose was repeated three hours after the initial testing and found to be 1.83 mmol/l. An automated complete blood count revealed mild thrombocytopenia of $141 \times 10^9/l$ ($175-400 \times 10^9/l$); however, a blood smear was not performed to determine whether clumping was present. Mild azotaemia with a blood urea nitrogen (BUN) of 13.39 mmol/l (5.71-12.85 mmol/l) and creatinine of 247.5 $\mu\text{mol/l}$ (70.7-212.2 $\mu\text{mol/l}$) was also noted. The cat was discharged with the recommendation to return in six days to re-evaluate the blood glucose level and establish a serum insulin level. The blood glucose six days later was found to be 1.94 mmol/l with a serum insulin level of 171 pmol/l. The cat was started on 2.5 mg oral prednisone once daily.

An abdominal ultrasound revealed chronic renal changes, including increased echogenicity and decreased corticomedullary differentiation of both kidneys. The liver and pancreas were of normal appearance. A moderate amount of echogenic debris was present within the urinary bladder and a sample of urine was collected.

Urinalysis and thoracic radiographs were unremarkable. Based on the clinical signs of hypoglycaemia and normal insulin levels, the presumptive differential was an insulinoma. The cat was then referred for an exploratory laparotomy. Before surgery the cat was medically managed with prednisone and fed small, frequent meals. Pre- and postoperatively, the cat was managed with 2.5% dextrose intravenous solution.

At surgery, there was a single, well-defined mass approximately 4 mm in diameter involving the left limb of the pancreas and several smaller masses along the cranial border. Excisional biopsies were performed to remove the masses. Care was taken to minimise handling and inadvertent trauma to the pancreas throughout the surgery. The remainder of the abdomen was grossly normal. The masses were submitted for histopathology.

The larger, solitary mass in the left limb of the pancreas was histopathologically reported as an islet cell carcinoma, while the multi-focal lesions along the cranial border were reported as nodular hyperplasia. The nuclei of the carcinoma cells were observed to be uniform and mitoses were rare. The islet carcinoma cells were minimally invasive into the surrounding tissues and there was normal tissue noted around the mass suggesting "clean" margins.

The cat was discharged two days following surgery, after an uneventful recovery with no documented hypoglycaemia. However, the cat was presented on emergency five days postoperatively because of anorexia and vomiting. A serum chemistry panel revealed an elevated alanine aminotransferase of 216 U/l (12-130 U/l), mildly elevated amylase of 2223 U/l (500-1500 U/l) and a mildly elevated lipase of 1466 U/l (800-1200 U/l). Mild azotaemia (BUN 14.7 mmol/l, creatinine of 236.9 µmol/l) was also present. The blood glucose was 8.46 mmol/l. At this time it was suspected that a mild pancreatitis had developed. No further diagnostic testing was performed at that time such as a trypsin-like immunoreactivity (TLI) or pancreatic lipase immunoreactivity (PLI) because of the length of time to obtain test results and financial constraints. Food was withheld from the cat for 24 hours and food was then slowly

reintroduced. Subcutaneous fluids were administered by the owners at home as needed.

Nine days postoperatively, the cat was presented to the referring veterinarian for suture removal. At that time the blood glucose was 8.88 mmol/l. The serum amylase (1620 U/l) returned to within normal limits. The blood glucose was monitored periodically over the next three weeks and was found to be within normal limits.

The cat has since been clinically normal with no neurological signs. The cat receives routine health care, but the owner has declined further monitoring for tumour recurrence such as abdominal ultrasound. The cat was last seen for a dental prophylaxis by the referring veterinarian 32 months postsurgery with no clinical signs of tumour recurrence.

DISCUSSION

This is the fifth reported case of islet cell carcinoma histopathologically diagnosed in the cat. Although insulinomas are rare, they are the most commonly diagnosed islet cell tumours in the dog, cat and ferret. It is important to include insulinoma as a differential diagnosis in any cat that is presented with persistent hypoglycaemia and seizure-like episodes, with concurrently normal to high insulin levels. If clinical signs are consistent with a possible insulinoma, but blood glucose or insulin levels are not, then evaluation of serum fructosamine levels may be of value (Mellanby and Herrtage 2002). Other causes of hypoglycaemia should be considered, including insulin overdosage, sepsis, hepatic disease, hypoadrenocorticism, portosystemic shunts and non-pancreatic insulin-secreting tumours (Feldman and Nelson 2004). It is important to aggressively treat the episodes of low blood glucose, because prolonged hypoglycaemia can lead to irreversible neurological complications (Kraje 2003).

The underlying aetiology of insulinomas in dogs and cats is unknown (Page 2001). Insulinomas are most commonly seen in older, large-breed dogs such as the German shepherd, boxer, standard poodle, Irish setter and retriever lines. There have not been enough reports of

insulinomas in cats to establish such breed or age predilections, but evidence to date indicates an increased incidence in older cats, as in this case. There are only four documented cases of insulinoma in the cat and one case was reported as an incidental finding at post-mortem examination (McMillan and others 1985, O'Brien and others 1990, Hawks and others 1992, Kraje 2003). Three of the five reported cases of insulinomas have been found in Siamese cats. Insulinomas are more commonly seen in male ferrets, but at this time there is no reported sex predilection in dogs or cats (Elie and Zerbe 1995). Most insulinomas in the dog and ferret are malignant with a high likelihood of metastasis present at the time of diagnosis. This may be true of the cat as well.

Abdominal exploration with excision of gross disease is the treatment of choice to palliatively treat insulinomas in the cat and dog (Tobin and others 1999). Medical management of insulinomas in the veterinary population includes the feeding of small, frequent meals and the use of glucocorticoids, diazoxide and somatostatin to antagonise or inhibit the production and/or secretion of insulin. Unfortunately, medical management has minimal efficacy and the potential for severe side effects. Other drugs that have been evaluated include various chemotherapeutic agents such as streptozotocin and alloxan, which have direct effects on the pancreatic beta cells (Moore and others 2002).

Of the five reported cases in cats, three insulinomas have been located in the left limb of the pancreas. The remaining two cases identified the tumour within the right limb and at the angle of the pancreas between the portal vein and the pancreatic duct. At this time, there is not enough data to conclude whether location of the tumour influences the diagnosis or prognosis. However, a tumour in either limb of the pancreas can be more easily resected and may be associated with a better prognosis. There has been no reported predisposition for tumour location in the pancreas in dogs (Feldman and Nelson 2004).

One of the most common complications reported postoperatively in the dog and cat is pancreatitis, as a result of manipulation of the pancreatic tissues. It is very

important to use atraumatic techniques and minimise intraoperative pancreatic manipulation to decrease the risk of postoperative pancreatitis. The cat in this report was suspected to have experienced pancreatitis. Pancreatitis is difficult to diagnose in the cat because of variable clinical signs and lack of specificity and sensitivity of serum amylase and lipase activity. Abdominal ultrasonography is a specific tool used to aid in the diagnosis of pancreatitis; however, it lacks sensitivity (Steiner 2003). Steiner also reported that in a group of cats with experimentally induced pancreatitis, both serum fTLI and fPLI concentrations did increase initially, but serum fPLI stayed elevated much longer than did serum fTLI concentration. This suggests that, as in the dog, serum PLI concentration is much more sensitive for pancreatitis than serum TLI concentration. It has been reported that a serum fTLI concentration greater than 100 µg/l is considered diagnostic for feline pancreatitis (Swift and others, 2000). It is important to note that a definitive diagnosis of pancreatitis can often only be made histopathologically by pancreatic biopsy at exploratory laparotomy or laparoscopy.

Diabetes mellitus as the result of inadequate insulin secretion from atrophied cells and persistent or recurring hypoglycaemia from metastatic or local recurrence of disease may also follow surgical excision. In one report, a week-long episode of hyperglycaemia with concurrent glucosuria in a cat was managed with protamine zinc insulin (O'Brien and others 1990). Periodic monitoring of blood glucose and abdominal ultrasonography may help to detect recurrence before the return of clinical signs in the affected cat. A limitation of this study is the lack of ultra-

sonographic follow-up postoperatively to evaluate for evidence of local recurrence or metastatic disease.

Of the five reported cases of insulinoma, one cat was euthanased one month postoperatively because of irreversible neurological complications (Kraje 2003). Case reports of insulinoma in the remaining cats document recurrence of clinical signs at five days, six days, seven months and 18 months postoperatively (McMillan and others 1985, O'Brien and others 1990, Hawks and others 1992, Kraje 2003). Only one post-mortem examination was performed on the cat surviving 18 months. Metastases to the pancreatic lymph nodes and liver were found at post-mortem examination (Hawks and others 1992). This case report is unique because of the fact that the cat has had no recurrence of clinical signs for a prolonged period postoperatively. Reasons for the long-standing survival may be a result of the relatively early detection and complete surgical excision of the insulinoma. Another interesting feature of this tumour is the lack of reported histological characteristics of malignancy, including uniform nuclei, rare mitotic figures and minimal invasion into surrounding tissue.

The key to successful management of this disease in the cat relies on early diagnosis based on clinicopathological abnormalities and prompt surgical resection of grossly involved tissues. The long-term prognosis for insulinoma in the cat is guarded as a result of the high likelihood of metastatic disease and the associated clinical signs.

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