Hypoglycemia and irreversible neurologic complications in a cat with insulinoma

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- Insulinoma is rare in cats.
- Immunohistochemical stains for chromogranin A and insulin can aid in the diagnosis of insulin-secreting neoplasms.
- In cats, chronic hypoglycemia can cause irreversible neurologic damage; prompt diagnosis and treatment of hypoglycemia are necessary.

A 14-year-old, 3.9-kg (8.6-lb) spayed female domestic shorthair cat was referred for evaluation because of weakness, lethargy, decreased appetite, diarrhea, and weight loss during a 2- to 3-week period. On the day of the initial evaluation, the cat had 2 grand mal seizures, each < 1 minute in duration. Anticonvulsant medication was not administered. Ten days prior to this evaluation, serum biochemical analyses revealed hypoglycemia (blood glucose concentration, 38 mg/dL; reference range, 64 to 170 mg/dL) and azotemia (BUN concentration, 44 mg/dL [reference range, 14 to 36 mg/dL]; creatinine concentration, 3.2 mg/dL [reference range, 0.6 to 2.4 mg/dL]). Results of a CBC were within reference limits. Total thyroxine concentration was low (< 0.2 µg/dL; reference range, 0.8 to 4.0 µg/dL).

On physical examination, the cat was weak, appeared depressed, disoriented, and was hypothermic (rectal temperature, 36.8°C [98.3°F]). On thoracic auscultation, bradycardia (heart rate, 92 beats/min) and an intermittent gallop rhythm were detected. Abdominal palpation revealed bilaterally small kidneys. The menace response was inconsistent; retinal examination revealed a small hyper-reflective area at the lateral aspect of the left tapetum. Serum glucose concentration at the time of examination was 20 mg/dL. Serum biochemical abnormalities included high concentrations of BUN (35 mg/dL; reference range, 20 to 30 mg/dL) and creatinine (3.1 mg/dL; reference range, 0.7 to 1.9 mg/dL). Results of a CBC were within reference limits. Serum testing for FeLV antigen and FIV antibodies yielded negative results; the cat was seronegative for feline infectious peritonitis virus and *Toxoplasma gondii*. Urinalysis revealed specific gravity of 1.024 and pH of 5.0. Serum bile acids concentration after withholding of food was 7.6 µmol/L, and the postprandial value was 12.3 µmol/L (reference range, 0 to 15 µmol/L). Abdominal radiographic and ultrasonographic examination confirmed that both kidneys were small. Thoracic radio-graphy and echocardiography revealed no abnormalities. Systolic blood pressure was 120 mm Hg. Insulin activity in the initial serum sample was 0.9 µU/mL (reference range, < 0.1 to 8.0 µU/mL); unfortunately, the serum sample was not frozen, which may have resulted in an artifactually low value.

Pending diagnostic testing results, the cat was hospitalized. Supportive care included IV fluids supplemented with dextrose (saline solution [0.45% NaCl] with 2.5% dextrose and 20 mEq of potassium chloride/L, administered at 15 mL/h), ampicillin (22 mg/kg [10 mg/lb], IV, q 8 h), enrofloxacin (5 mg/kg [2.3 mg/lb], IV, q 24 h), external heat support, and monitoring of blood glucose concentration, rectal temperature, and heart rate. Differential diagnoses for hypoglycemia in this cat included an insulin-secreting neoplasm (pancreatic or extrapancreatic), sepsis, and hepatic disease. Extrapancreatic neoplasia was considered less likely because of the lack of masses or organomegaly detected on physical, radiographic, and ultrasonographic examinations. Sepsis was also considered to be less likely because of the normal hematologic findings, absence of a nidus of infection on radiographic or ultrasonographic examination, and lack of response to IV administration of broad-spectrum antimicrobials. Because hepatic variables were within reference limits on serum biochemical analyses, hepatic disease was similarly considered to be less likely. However, detection of normal insulin activity, despite profound hypoglycemia, was consistent with, although not diagnostic for, an insulin-secreting neoplasm.

Medical management for a suspected insulinoma was continued and included prednisone (0.5 mg/kg [0.23 mg/lb], PO, q 12 to 24 h) and frequent forced alimentation. Substantial improvement in blood glucose concentration was not observed. An exploratory laparotomy was subsequently performed to evaluate the pancreas for neoplasia and place a gastrostomy tube to aid in the frequent alimentation. During surgery, a 1.5- to 2-cm, raised tan pancreatic mass was identified at the apex of the left limb of the pancreas. No other gross lesions were identified during surgical examination of the abdomen. The mass was resected, and a 16-F gastrostomy tube was placed. Histologic examination of the mass revealed a nodular epithelial pancreatic neoplasm with mild multifocal lymphoplasmacytic inflammation of the surrounding pancreatic tissue. Immunohistochemical staining revealed diffuse positive staining for chromogranin A and patchy positive staining for insulin. Chromogranin A is a neuroendocrine marker; therefore, the positive staining of the pancreatic tumor demonstrated that the tumor was of endocrine (islet cell) origin.[1] These findings confirmed the presence of an islet cell insulin-secreting neoplasm in the cat of this report.

Blood glucose concentration was within reference limits (varying from 85 to 236 mg/dL) after surgery,

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which confirmed the successful removal of the insulin-secreting neoplasm. However, the cat's menace response remained inconsistent, and its appetite was minimal. At discharge 7 days after surgery, the cat was intermittently pacing and disoriented. Periactin (0.5 mg/kg, PO, q 12 h) and prednisone (0.5 mg/kg, PO, q 24 h) were administered in an attempt to stimulate the appetite, with minimal improvement. Hematologic and serum biochemical analyses were repeated, and a serum **trypsin-like immunoreactivity (TLI)** assay was performed to rule out the development of pancreatitis after surgery. No notable abnormalities were identified via serum biochemical examination, and the serum TLI value was unremarkable (51 µg/L; reference range, 12 to 82 µg/L). Approximately 1 month after discharge, the cat was still not eating unaided; it continued to appear disoriented and have an inconsistent menace response, and its behavior became aggressive. No additional abnormalities were found on repeat physical examination. After withholding food, serum insulin activity was 3.6 µU/mL, and serum glucose concentration was 97 mg/dL. This activity of insulin was considered appropriate for a normal serum glucose concentration; thus, the possibility of functional metastatic disease seemed unlikely. After feeding, serum ammonia and glucose concentrations were within reference limits. The owner declined additional diagnostic testing, and the cat was euthanatized. Necropsy examination was declined.

Insulinomas are endocrine tumors of pancreatic β cells. These tumors have rarely been reported in cats. Four cats have been reported[2-6] to have histologically confirmed insulin-secreting pancreatic tumors. Those cats were not young (12, 14, 16, and 17 years old); 3 were castrated male Siamese, and 1 was a castrated male domestic longhair. Among the 4 cats, clinical signs included seizures (n = 2), staggering with muscle fasciculations (1), and weight loss with polydipsia (1).

Clinical signs associated with insulinomas are typically secondary to hypoglycemia and include seizures, weakness, ataxia, mental dullness, disorientation, and collapse.[5-8] Seizures are the most common clinical sign in affected animals. Episodes of hypoglycemia can be interspersed by periods of normoglycemia because of the effect of counter-regulatory hormones, such as epinephrine, glucagon, cortisol, and growth hormone. These hormones antagonize the effects of insulin and stimulate gluconeogenesis and glycogenolysis, thereby creating a compensatory increase in blood glucose concentration and variable clinical signs.

Differential diagnoses for hypoglycemia in cats that are not receiving insulin or hypoglycemic medications include insulinoma or other insulin-secreting neoplasm, hepatic disease, sepsis, hypoadrenocorticism, storage diseases, and neonatal hypoglycemia. The diagnosis of hypoglycemia is typically straightforward; however, certain cats may require a period during which food is withheld before serum glucose concentration declines. The most common manner in which an insulin-secreting tumor is diagnosed is via demonstration of hypoglycemia (ie, blood glucose concentration < 60 mg/dL) with concomitant normal-to-increased serum insulin activity. Most of the other causes of hypoglycemia are associated with low insulin activity, because the regulation of insulin secretion is under normal control. Nuclear scintigraphy with radiolabeled somatostatin analogs has had limited application in veterinary medicine to date but can aid in diagnosis, presurgical planning, and prognostic assessment. The expense and availability of this diagnostic modality primarily limit its use.[9]

Treatment of insulinomas includes surgical and medical management. Surgical exploration of the abdomen to identify and remove abnormal pancreatic tissue is often the first goal of treatment. Results of a study[8] of clinical outcomes in dogs with insulinomas that were treated either surgically or medically indicate a significantly longer survival time after surgical treatment. At present, surgical removal of the pancreatic neoplasm is the recommended treatment in dogs suspected to have insulinomas.[8] If the entire mass cannot be removed, debulking it may improve glycemic control through reduction in insulin production. If a pancreatic mass cannot be identified during surgery, partial pancreatectomy may be performed. The main surgical complication of any pancreatic surgery is the development of pancreatitis. To prevent this, most animals are treated prophylactically during the immediate postoperative period with IV fluids and withholding of food. Surgical exploration of the abdomen can also be helpful in prognostic assessment, as many of these pancreatic tumors have metastasized by the time of diagnosis.

Medical management can be used as an adjunctive treatment when clinical signs recur after surgery or as the sole treatment in those animals for which surgery is not elected or recommended. Frequent feedings of a high-protein, high-fat, high-complex carbohydrate diet is then indicated.[5-8] If dietary management alone does not result in sufficient improvement of clinical signs, prednisone can be administered.[5-8] Prednisone stimulates gluconeogenesis and glycogenolysis by the liver and inhibits glucose utilization by cells. If prednisone-related adverse effects are too severe or glycemic control is not improved, diazoxide may be administered (either alone or in combination with prednisone).[7] Diazoxide directly inhibits insulin secretion, stimulates production of glucose by the liver, and inhibits glucose uptake by cells.[6,10,11] However, to the author's knowledge, there are no reports of treatment with diazoxide in cats. A somatostatin analogue (octreotide) has been used in dogs with insulinomas with variable success.[12] Octreotide is thought to block insulin secretion.[12] The chemotherapeutic agent streptozotocin has been used before and after surgery in dogs with insulinomas.[7,11,13] To the author's knowledge, there are no reports of administration of streptozotocin in cats with insulinomas. Because of the risk of renal failure associated with administration of this agent, its use was not considered in the cat of this report, which had preexisting renal azotemia.

In the cat of this report, chronic hypoglycemia was believed to have caused neurologic lesions that were not reversible with return of control of the serum glucose concentration and which led to the cat's abnormal and aggressive behavior. There is a report[14] in which brain lesions in a dog with hypoglycemia secondary to an insulinoma are described; neuronal death in the superficial layers of the cerebral cortex and the dentate gyrus of the hippocampus

were found. It was proposed that these lesions resulted from ischemic-type neuronal cell death caused by the release of excitatory amino acids (specifically glutamate and aspartate) as a result of hypoglycemia.[14] The hippocampus is part of the telencephalon and involved in regulation of the limbic system.[15] In humans, disease of the hippocampus can lead to psychomotor convulsions, fear, arousal, rage, and hallucinations.[15] The degree of neuronal damage is likely related to the chronicity and severity of hypoglycemia. It is suggested that (at least initially) the neuronal changes are reversible; therefore, rapid diagnosis and treatment of hypoglycemic conditions are of critical importance.[14]

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