Insulin-Secreting Pancreatic (Islet Cell) Carcinoma in a Cat

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A functional, insulin-secreting pancreatic (islet cell) carcinoma was diagnosed in a 17-year-old male Siamese cat. Diagnosis was made on the basis of clinical signs (i.e., seizures and stupor) that resolved temporarily after correction of hypoglycemia with feeding or intravenous administration of glucose, the finding of an inappropriately increased serum insulin concentration in the face of hypoglycemia, and prolonged resolution of hypoglycemia after surgical removal of the tumor. Primary islet cell tumor of the pancreas was confirmed by biopsy. The cat died 18 months later, and necropsy revealed metastases to regional lymph nodes and liver. Specimens of the tumor and metastatic lesions both stained positively for insulin. (Journal of Veterinary Internal Medicine 1992; 193–196)

INSULIN-SECRETING pancreatic (islet cell) tumors leading to hypoglycemia are well recognized in human beings,[1] dogs,[2–5] and ferrets,[6] but they have not been well documented in cats. This report describes the clinical, serum biochemical, and pathologic findings in an elderly cat with an insulin-secreting tumor of the pancreas.

Materials and Methods

Serum insulin was measured with a commercial radioimmunoassay kit.* Assay of serial dilutions of a feline serum pool containing increased insulin concentrations (approximately 400 pmol/L) resulted in inhibition curves with slopes parallel with the standard curve. Accuracy was determined by adding various quantities of purified pork regular insulin to a feline serum pool containing an undetectable concentration of insulin; analysis of the resulting data revealed an average recovery of 94%. The sensitivity of the insulin assay was 35 pmol/L. The intra- and interassay coefficients of variation were 8.1% and 14%, respectively.

Immunocytochemical staining was done with the avidin-biotin-peroxidase complex immunoperoxidase method as previously described,[7,8] with polyclonal antibodies against guinea pig insulin,† porcine glucagon,† human gastrin,† pancreatic polypeptide,† and somatostatin† and bovine neuron specific enolase,† and chromogranin A.‡

Case Report

A 17-year-old male castrated Siamese cat was examined because of previously diagnosed hypoglycemic seizures. The seizures were grand mal, unassociated with meals, and responsive to oral corn syrup. The seizures had begun 18 months previously and were increasing in frequency.

Three and 11 months before examination, the cat had two episodes of severe regenerative anemia (PCV = <10%). Tests for FeLV, FIP, toxoplasmosis, and hemobartonella were negative. During hospitalization for the second episode of anemia, the cat was found in a stupor with a blood glucose concentration of 25 mg/dl (normal, 70–150 mg/dl). The cat responded well to intravenous administration of dextrose, and was discharged with instructions to the owner to feed frequently and to administer corn syrup as needed to control the seizures. Prednisone (5 mg, once daily, orally) was also given for 1 month. During prednisone administration, the seizures decreased in frequency and severity but then increased

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to two or three seizures per week. Two weeks before examination, at the time of one of the seizures, determination of serum glucose and insulin concentrations by the referring veterinarian revealed moderate hypoglycemia (50 mg/dl) with severe hyperinsulinemia (900 pmol/L; normal serum insulin = 35–220 pmol/L).§

On physical examination, the cat was weak, depressed, and hypothermic (temperature, 37.4 C). Severe hypoglycemia was confirmed (blood glucose, 18 mg/dl) and the cat's weakness and depression resolved immediately after feeding. The serum insulin concentration again was increased (250 pmol/L). Abdominal and thoracic radiographs were unremarkable, but abdominal ultrasonography showed a 1-cm mass in the angle of the pancreas adjacent to the portal vein. There was no evidence of metastasis to the liver or mesenteric lymph nodes. These findings were consistent with a diagnosis of insulin-secreting pancreatic (islet cell) tumor.

Exploratory laparotomy was completed, and a solitary, 1-cm in diameter, pale, nodular mass was excised from the angle of the pancreas between the portal vein and the pancreatic duct. No metastic tumor was seen in the liver or regional lymph nodes. Blood glucose concentrations remained normal during and several days after surgery, despite discontinuation of dextrose administration. The serum concentrations of insulin (140 pmol/L) and glucose (150 mg/dl) were normal 10 days after surgery.

On histologic examination, the mass was consistent in appearance with an islet cell carcinoma. It was composed of a monomorphic population of round to oval cells with abundant, pale, finely granular eosinophilic cytoplasm and round to oval vesicular nuclei. Mitotic figures were uncommon, and tumor cells were subdivided into small nests and islands by a delicate fibrovascular stroma. The tumor was partially encapsulated and caused mild compression of the surrounding exocrine parenchyma. Metastasis was not observed on examination of submitted liver sections. Immunocytochemical staining of the tumor revealed diffuse positive staining for insulin, neuron specific enolase, and chromogranin A, with rare, scattered cells staining positively for glucagon and somatostatin.

At the 6-month reexamination, the cat was clinically normal and had normal serum concentrations of glucose (70 mg/dl) and insulin (200 pmol/L). Ten months after surgery, the cat began to have grand mal seizures again. At that time, determination of paired serum glucose and insulin concentrations again revealed hypoglycemia (46 mg/dl) and hyperinsulinemia (357 pmol/L), consistent with a recurrent insulin-secreting tumor of the pancreas. The owner resumed administration of prednisone (5 mg, once to twice daily, orally) and corn syrup and frequent feedings, but intermittent seizures continued.

At 18 months, the cat developed anorexia, ataxia, and was described as dazed by the owner. Results of serum biochemical analysis revealed increased values for alanine aminotransferase (1870 IU/L; normal = 5–75 IU/L), aspartate aminotransferase (1000 IU/L; normal = 5–60 IU/L), alkaline phosphatase (161 IU/L; normal = 1–70 IU/L, total bilirubin (1.2 mg/dl; normal = 0.1–0.6 mg/dl), and amylase (5880 IU/L; normal = <3000 IU/L). Hypoglycemia (54 mg/dl) and hyperinsulinemia (240 pmol/L) were again present. The cat initially responded to supportive treatment (i.e., subcutaneous fluids), but was found dead in the cage on the third day of hospitalization.

Results of necropsy revealed metastases to the pancreatic lymph nodes and liver. Histopathologic examination revealed that the metastatic lesions were similar in appearance to the primary tumor, and results of immunocytochemical staining revealed diffuse positive staining for insulin, neuron specific enolase, and chromogranin A, with rare cells staining positively for pancreatic polypeptide, somatostatin, and glucagon (Figs. 1, 2). Examination of liver also revealed severe, diffuse, suppurative, chronic-active cholangiohepatitis with bridging portal fibrosis and bile stasis. Moderate diffuse chronic-active pancreatitis, with marked fibrosis and nodular hyperplasia of the exocrine pancreas, was also observed.

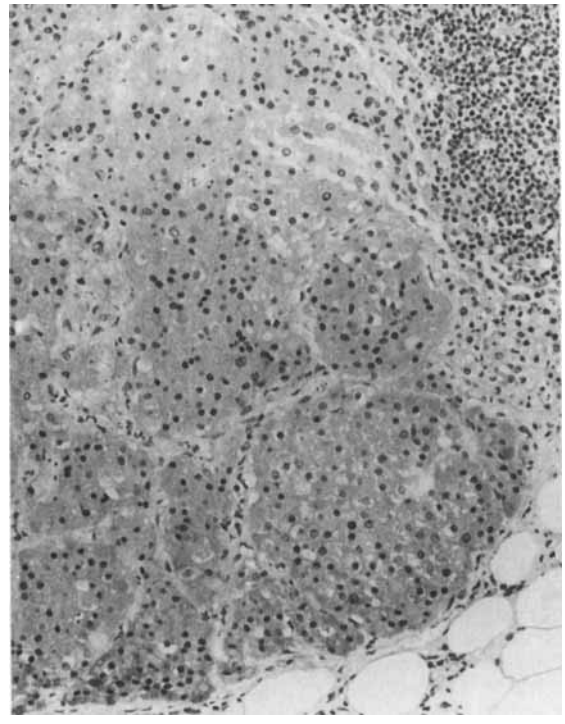

FIG. 1. Section of lymph node containing metastatic islet cell tumor. Immunohistochemical stain with anti-insulin (×160). Note the immunoreactive tumor cells with positive cytoplasmic staining.

§ To convert from pmol/L to mIU/ml, divide given value by 7.18.

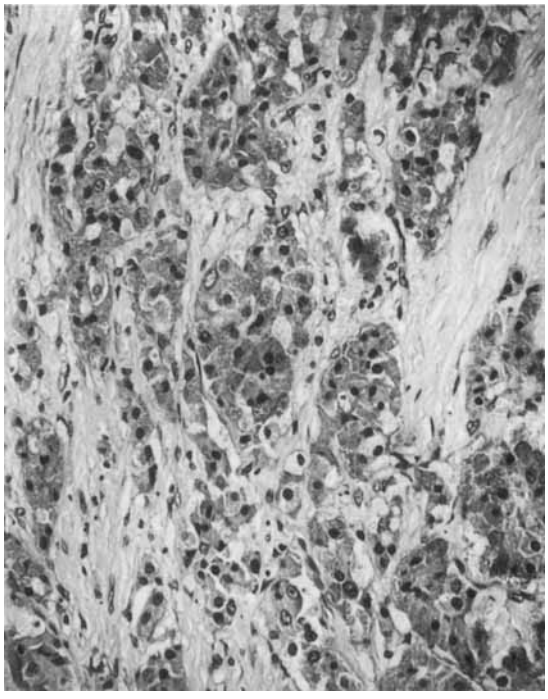

FIG. 2. Section of lymph node containing metastatic islet cell tumor. Immunohistochemical stain with anti-chromogranin A (×256).

Discussion

Functional, insulin-secreting islet cell neoplasms of the pancreas (i.e., insulinomas) have been reported in human beings and a variety of domestic animals.[1-6] Insulinomas are the most frequently reported pancreatic endocrine neoplasm in people, the vast majority (90%) of which are benign (adenomas).[1] Similarly, insulin-secreting tumors are the most common islet cell tumor in dogs, but, in contrast to humans, most are malignant (carcinomas), and approximately half metastasize to the regional lymph nodes and liver.[2-5] In cats, insulin-secreting pancreatic (islet cell) tumors are rare and have not been well characterized. Only three have been confirmed by histopathologic findings, in addition to clinical and biochemical evidence of hypoglycemia.[9-11] In one of these cats, a 12-year-old Siamese, severe hypoglycemia (20 mg/dl) and seizures resolved after surgical removal of a 1-cm islet cell tumor.[9] However, clinical signs associated with hypoglycemia recurred 6 days after surgery, suggesting the presence of residual insulin-secreting tumor. The owners refused further treatment, and the cat died of seizures 5 weeks after surgery; necropsy was not allowed. The second cat, a 16-year-old domestic longhair, had clinical signs of weight loss, polydipsia, and loss of appetite.[10] Physical examination revealed a large, cranial abdominal mass, and laboratory testing showed hypoglycemia (31 mg/dl). Surgical excision of a large nodular mass involving the right limb of the pancreas was attempted, but the cat developed cardiac arrest and died. Histopathologic examination revealed a ductal pancreatic adenocarcinoma, as well as two small islet cell tumors, 0.5 and 0.7 cm in diameter. Immunocytochemical staining of the islet cell tumors was positive for insulin in many cells, with fewer glucagon-containing cells.[10] The third cat, a 14-year-old Siamese, had a 4-month history of episodic staggering and leg and facial twitching.[11] Laboratory testing revealed mild hypoglycemia (59 mg/dl) and hyperinsulinemia, and intravenous glucose tolerance testing showed delayed and exaggerated insulin secretion. Surgical removal of a 2-cm mass from the left lobe of the pancreas resulted in clinical remission of hypoglycemia for 7 months. Histopathologic examination revealed a malignant pancreatic tumor, and immunocytochemical staining was positive for insulin in more than 50% of the cells, with less than 10% of the tumor cells positive for somatostatin and islet amyloid polypeptide.[11]

In our cat, the diagnosis of insulin-secreting pancreatic (islet cell) tumor was made on the basis of the following: 1) neurologic signs (i.e., seizures and stupor) associated with severe hypoglycemia; 2) temporary relief of clinical signs after correction of hypoglycemia with feeding or intravenous administration of glucose; 3) the finding of an inappropriately increased serum insulin concentration in the face of hypoglycemia on numerous occasions; 4) prolonged resolution of neurologic signs (i.e., convulsions) after surgical removal of the primary tumor, with concurrent normalization of serum glucose and insulin concentrations; and finally, 5) histologic confirmation of a pancreatic islet cell carcinoma with metastases to regional lymph nodes and liver, both of which stained positively for insulin as well as for neuron specific enolase and chromogranin A, two immunohistochemical markers for normal and neoplastic cells of neuroendocrine origin.[7,8] As in this case, most islet cell tumors in humans and dogs are multihormonal when examined by immunocytochemical staining, but clinical signs due to oversecretion of one hormone usually predominate.[4]

Early in the course of illness, the cat developed severe regenerative anemia on two occasions. The cause of this anemia was not determined, and it is not known if the anemia was in any way related to the insulin-secreting pancreatic (islet cell) tumor. Anemia certainly is not a finding associated with insulinomas in human patients or dogs.[1,3,5] However, after surgical removal of the primary islet cell tumor, recurrence of the anemia was not observed during the final 18 months of the cat's life.

Treatment of insulin-secreting pancreatic (islet cell) tumor may include medical management, surgical excision, or both. In our cat, frequent feedings and daily administration of glucocorticoids, which act to increase hepatic gluconeogenesis and decrease tissue utilization of glucose, helped control hypoglycemia and associated clinical signs, but surgical removal of the primary islet

cell tumor successfully controlled the hypoglycemia for months. As in dogs with islet cell carcinoma, in which tumor regrowth and metastases and return of clinical signs of neuroglycopenia are almost inevitable,[2,3,5] recurrence developed in this cat 10 months postoperatively, and metastases to the regional lymph nodes and liver were documented at necropsy.

The cause of death in this cat is unclear, but was likely related to the cat's severe cholangiohepatitis and chronic pancreatitis, rather than to complications of the islet cell carcinoma. Although the pancreatitis might have been related to the previous pancreatic surgery, the long interval between surgery and death in this cat make this less likely. The pancreatitis may have been related to the liver disease since a frequent coincidence of cholangiohepatitis and pancreatic disease has been reported in cats.[12]

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