

PANCREATIC NEOPLASIA
Adenocarcinoma
"Insulinoma"/Hypoglycemia
"Gastrinoma"

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PANCREATIC NEOPLASIA

Neoplasms of the pancreas arise primarily from epithelial tissue (Table 155-7). The two most important neoplasms are pancreatic adenocarcinoma and pancreatic islet cell adenocarcinoma. Neoplasms of the pancreas are uncommon in both dogs and cats. Estimates on their frequency of occurrence are from 0.05 to 1.88 per cent of all cancers in dogs¹⁴⁵ and from 1.1 to 2.8 per cent of all cancers in the cat.^{99, 124} Adenocarcinomas are strongly associated with increasing age. Mean age of occurrence is 10 years in dogs (range 5 to 16 years) and 12 years in cats. Cats over 15 years old have an especially high risk. The only canine breed identified to be at increased risk is the Airedale.

Pancreatic Adenocarcinomas

Pancreatic adenocarcinomas arise from both ductular and acinar tissue of the exocrine pancreas. Ductular carcinomas are thought to predominate.⁶⁹ These tumors metastasize readily, frequently prior to clinical diagnosis. Metastases occur most often in the liver, retroperitoneum, and mesenteric lymph nodes.⁹⁹ Less common metastatic sites include the lung, duodenum, adrenal, kidney, heart, and gallbladder.

Clinical signs noted are often nonspecific and frequently relate more to the primary metastatic site (liver) than the organ of origin. Weight loss, anorexia, depression, vomiting, and jaundice are common.⁴ Pancreatic adenocarcinomas frequently compress the common bile duct, producing jaundice (Fig. 155-8). Signs of maldigestion have been reported in association with pancreatic adenocarcinomas, but this phenomenon appears to be rare.⁸⁹ These tumors are generally small and rarely palpable in dogs, but in cats, a cranial abdominal mass is often detected.²¹

A definitive antemortem diagnosis is rarely made except via exploratory celiotomy. These animals often die or are euthanized with the diagnosis established at necropsy. Serum amylase and lipase concentrations are usually normal, except in cases where rapidly invading tumors produce mild signs of pancreatitis. Biochemical profiles most often suggest that liver, rather than pancreatic disease is present. Mild increases in ALT, with moderate to marked rises in SAP and serum bilirubin are typical of metastatic pancreatic adenocarcinoma. Radiographs may detect evidence of mass lesions, peritoneal

fluid accumulation or carcinomatosis.⁴ Abdominocentesis, with or without lavage, may be helpful in establishing a diagnosis. Pancreatic adenocarcinomas exfoliate readily, and cytology of peritoneal fluid often supports a diagnosis of abdominal malignancy. Cytological evaluations rarely establish the site of origin for the exfoliated carcinoma cells, but the prognosis is not altered.

The prognosis for animals with pancreatic adenocarcinoma is invariably poor owing to the tendency for early and widespread metastases. Occasional cases in man have responded to 5-fluorouracil. The therapy for solitary lesions is surgical removal.

Pancreatic Adenoma/Hyperplasia

Pancreatic hyperplasia is considered a frequent finding in aged dogs and cats.^{21, 99} Pancreatic adenoma is rare, although precise microscopic criteria for separation of these two entities are equivocal.^{69, 99} These lesions appear as small white to tan nodules within the pancreas rarely larger than 1 to 4 mm, and have no clinical significance.

Pancreatic Islet Cell Tumors

Two major pancreatic islet cell neoplasms have been recognized. The most common is the so-called insulinoma or functional tumor of the pancreatic beta cells. A much less commonly recognized neoplasm, the gastrinoma, has also been reported. Gastrinomas are islet cell tumors arising from pancreatic G-cells which secrete gastrin. Neither of these neoplasms occurs with any frequency in the cat.^{69, 91}

Insulinomas

So-called insulinomas are much less frequently recognized than pancreatic acinar cell carcinomas. Approximately 200 cases had been reported up until 1990, with very few cases documented in cats.^{21, 22, 69, 91, 92, 128} Between 60 and 70 percent of these neoplasms are functional. Although the term *insulinoma* is commonly applied to these neoplasms, the vast majority are islet cell carcinomas.^{69, 140} Even tumors which appear benign microscopically often develop recurrent signs of disease at variable intervals post-operatively

due to the presence of metastases that were not identified at surgery. The mean age of occurrence is between 9 and 10 years of age with a range between 4 and 15 years old.^{22, 49, 78, 139} Large breeds of dogs that appear to be at increased risk include Irish setters, golden retrievers, boxers, German shepherds, standard poodles, fox terriers and mix breeds.^{73, 78, 92, 102, 124} Seventy-two percent of affected dogs weigh greater than 25 kg.⁷⁸ No sex predilection exists.

Clinical signs are highly variable, but are all related to hypoglycemia induced by excessive production of insulin by the tumor, and/or to catecholamine release secondary to hypoglycemia. Hypoglycemic convulsions or collapse may be seen in 2/3 of dogs with insulinomas but weakness and ataxia, particularly of the rear limbs, muscle tremors, dullness, disorientation, and decreased exercise tolerance are also common.^{22, 24, 73, 92, 139} The rate of drop in blood glucose concentration rather than the absolute value determines the type and severity of signs. A rapid fall in blood glucose generally results in signs of catecholamine release (weakness, hunger, tachycardia) while a slower drop generally is associated with neurological manifestations.^{102, 153} The duration of clinical signs prior to diagnosis ranges from 1 day to 3 years, with a mean of 3 months.^{22, 73, 92} Nearly one-third will have been treated non-specifically for an idiopathic seizure disorder prior to diagnosis.^{22, 92} Signs are nearly always intermittent and long periods of time may elapse between episodes of clinically apparent hypoglycemia. Signs become more frequent as the disease progresses. Generally, a poor correlation exists between the time an animal is fed and the onset of clinical signs.

Confirming a diagnosis of insulinoma is relatively uncomplicated in the majority of cases. Routine hematologic, biochemical and urinalysis findings in these patients are usually normal except for fasting or non-fasting hypoglycemia. The majority of cases have blood glucose values less than 70 mg/dl on initial evaluations.^{22, 51, 73} Once hypoglycemia is confirmed, the next step is to validate that it is due to relative or absolute insulin excess and not some other cause. Multiple potential rule-outs exist for hypoglycemia in dogs and cats and they must be simultaneously searched for in the work-up of the hypoglycemic animal.

Differential Diagnosis for Hypoglycemia

Increased Utilization	Decreased Production/availability	Miscellaneous
Insulinoma	Hepatic failure	Insulin overdosage
Extra-pancreatic neoplasia	Hypoadrenocorticism	Lab artifact
Sepsis	Uremia	
Exertional hypoglycemia	Starvation	
Polycythemia	Hypopituitarism	
Pregnancy	Hypothyroidism	
	“Puppy hypoglycemia”	
	Malabsorption	
	Glycogen storage diseases	

Serum should be analyzed for insulin concentration from any sample that is hypoglycemic in which another obvious cause for the hypoglycemia is not identified. Normal fasting serum immunoreactive insulin (IRI) concentrations range from 5 to 26 micro-units/ml from most veterinary laboratories.^{52, 102} The mean fasting IRI concentration in one large series of cases was 71.4 micrograms/ml.²² Approximately 75% of cases will have elevated serum IRI concentrations when initially evaluated and a diagnosis of insulinoma is highly likely. In the remaining 25% of cases in which initial IRI values are in the normal range, support for a presumptive diagnosis of insulinoma may be made by comparing the ratio between blood glucose and insulin in a number of ways. When these ratios are abnormal, they support a relative excess of insulin to glucose in peripheral blood. Comparisons may be made between the ratio of insulin to glucose (I/G), between the ratio of glucose to insulin (G/I), or by calculating an amended insulin glucose ratio (AIGR). Values supporting relative insulin excess for I/G are >0.23 micro-units/mg, for G/I are <3.31 mg/micro-unit, and for AIGR are >30 micro-units/mg.^(9 new) The AIGR is calculated as follows:

$$\text{AIGR (micro-units/mg)} = \frac{\text{Serum Insulin (micro-units/ml)} \times 100}{\text{Plasma Glucose (mg/dl)} - 30}$$

In most studies, if the blood glucose is less than or equal to 30 mg/dl, 1 has been substituted for the denominator. Utilizing the latter calculation for determining the AIGR increases the sensitivity of this ratio but decreases its specificity.^{42, 51, 70, 78} This results in more false positive diagnoses being made, and potentially, unnecessary surgery being performed. If hypoglycemia is not detected on random blood samples, and insulinoma is still suspected, several provocative tests can be performed to stimulate neoplastic islet cells to release insulin and induce hypoglycemia. These include "prolonged" fasting, intravenous

or oral glucose tolerance tests, L-Leucine tolerance, glucagon tolerance and tolbutamide tolerance tests. All the provocative tests, except fasting, are expensive, time consuming, unreliable, or carry high risk (tolbutamide tolerance), while not improving upon diagnostic accuracy. Most dogs with insulinoma can be made hypoglycemic by simple fasting for 8 to 12 hours or less.^{49, 51, 73, 139} When fasting dogs to induce hypoglycemia, testing should be started in the morning so they may be monitored throughout the day. Blood glucose measurements are made every 2 to 3 hours until hypoglycemia (< 60 mg/dl) is detected.⁴⁹ A serum IRI concentration is measured on the first hypoglycemic sample and an AIGR, I/G or G/I ratio calculated if necessary. Patients should be monitored closely throughout the testing period, particularly if seizures are the primary presenting complaint. Once hypoglycemia associated with hyperinsulinism is confirmed, exploratory surgery should be recommended. In situations where serum insulin assays are not available, exploratory surgery should be considered if other known causes for hypoglycemia have been eliminated (Table 155-8). Routine survey radiographs of the abdomen are of no diagnostic value as these neoplasms are too small to be detected.^{49, 92} Ultrasonography may be able to identify primary tumors within the pancreas or metastases in adjacent organs.⁴⁹ Thoracic radiographs are consistently negative for pulmonary metastases, even if present, and do not aid in staging the disease.^{49, 92}

Preoperative management of dogs with insulinomas varies depending on the severity of hypoglycemia and the presence or absence of other clinical signs (seizures, weakness, collapse, etc.). Feeding 3 to 6 small meals/day of a diet high in protein and complex carbohydrates often reduces or eliminates clinical signs. Semi-moist diets high in simple sugars should be avoided. The addition of prednisone and/or the oral hyperglycemic agent diazoxide, may also help stabilize patients preoperatively that fail to respond to frequent feedings alone. Hypoglycemia may be so severe that intravenous 5% or 10% dextrose may be needed to maintain blood glucose concentrations in the normal range, even though the patient is eating.

In occasional animals persistent symptomatic hypoglycemia will occur in spite of aggressive IV dextrose administration. In these cases, glucagon may be given as a constant rate infusion (CRI) to counteract the effects of the neoplastic insulin production. Reconstitute a 1 mg vial of glucagon, then mix the solution in a 1 liter bag of 0.9% saline and label the concentration as 1000 ng/ml. Keep the

glucagon solution refrigerated (good at least 72 hours). If the patient is severely neurologically compromised, an IV bolus of glucagon may be given at 50 ng/kg (0.05 ml/kg). Start the constant rate infusion with a syringe pump at 5 ng/kg/min. (0.3 ml/kg/hr). Check blood glucose after 15 minutes. If still hypoglycemic, increase the CRI to 10 ng/kg/min. (0.6 ml/kg/hr), and check the blood glucose again in 15 minutes. If still hypoglycemic, increase the glucagon dosage to 15 ng/kg/min. (0.9 ml/kg/hr) and recheck blood glucose concentrations in 15 minutes. If hypoglycemia is still present, add 2.5% dextrose to the infusion as well. This drug can be very effective in controlling symptomatic hypoglycemia when other medical therapy fails.

Patients are held off food 8 to 12 hours preoperatively and blood glucose concentrations are maintained by intravenous 5% dextrose. At exploratory surgery, the pancreas is gently but thoroughly palpated for evidence of tumor nodules. Nearly all cases will have readily identifiable, round, 1 to 2.5 cm diameter solitary (85% of cases) or multiple tumor nodules visible within the pancreas (Fig. 155-9).^{22, 51} Unfortunately, approximately 45% of patients will also have metastases to regional lymph nodes or the liver identified at surgery.^{22, 92} Tumors are identified with equal frequency within the left (splenic), or right (duodenal) limb of the pancreas. Much less commonly identified sites are the body or angle of the pancreas, and rare, diffuse, non-palpable tumors have been reported.^{51, 73} An isolated case of a primary ectopic insulinoma localized to the duodenal wall has also appeared.¹³⁶

It has recently been reported that intravenous methylene blue (Methylene blue Injection 1%, Elkins-Sinn Co., Cherryhill, NJ, 08034) may aid in identification of primary and metastatic insulinomas in dogs.^{53, 54, 136} Methylene blue intensely stains neoplastic islet cells helping to differentiate them from surrounding normal tissue. Three milligrams/kg are diluted in 250 ml of 0.9% sterile saline and given over 30 to 40 minutes. Maximal staining of the tumor occurs approximately 30 minutes after the infusion is begun. Hemolytic anemia may develop if this dosage is exceeded due to Heinz body formation. If no primary tumor is identified and the diagnosis is highly likely, it has been suggested to consider a blind resection of 50% of the pancreas in case diffuse islet cell neoplasia is present.⁵¹

The postoperative course for dogs with insulinomas is highly variable. Recognized complications include persistent hypoglycemia, surgically induced pancreatitis, diabetes mellitus, acquired epilepsy, and diffuse polyneuropathy.^{22,}

24, 49, 51, 92, 133 Persistent hypoglycemia develops in dogs in which the primary tumor is inoperable or metastases are present at surgery. This complication is reported in 20 to 27% of cases.^{22, 92} As much tumor as possible should be removed surgically, as this will modify the severity of postoperative hypoglycemia even though there is no chance for a cure.

Unlike humans, pancreatitis is an infrequent complication in dogs. Patients with signs of pancreatitis should be held off oral food and water for 36 to 48 hours. Intravenous 5% dextrose is only necessary if hypoglycemia persists during the postoperative period. Otherwise, balanced fluid and electrolyte solutions and broad spectrum antibiotics are administered.

Development of diabetes mellitus is a unique paradox of this disease. It has been hypothesized that prolonged increases in tumor insulin and subsequent hypoglycemia leads to atrophy of normal islet tissue. Partial pancreatectomy to control the tumor may also decrease insulin reserves. Diabetes may develop in 15% to 29% of dogs in the postoperative period.^{22, 49, 50, 92} In many cases the hyperglycemia is transient lasting from a few days to 2 months. In others the condition may last for years and require chronic insulin therapy. Gradual growth of metastases often results in correction of the diabetes over time. Eventually, signs of hypoglycemia will recur. These dogs need careful monitoring since signs of insulin overdosage and tumor reoccurrence are similar.

Rarer complications of insulinomas are acquired epilepsy and chronic diffuse polyneuropathy.^{10, 24, 49, 133} Recurrent severe hypoglycemia is hypothesized to result in organic brain damage that subsequently serves as a seizure focus, even though hypoglycemia is corrected. The seizures in some of these dogs will respond to therapy with anticonvulsants.

Occasional dogs will have persistent moderate to severe ataxia even though hypoglycemia has been corrected.^{10, 24, 49, 133} A peripheral polyneuropathy has been recognized in dogs with insulinomas characterized by decreased patellar reflexes, decreased conscious proprioception and electromyography findings compatible with axonal degeneration.

Medical management of dogs with insulinomas should be considered in a number of instances. It is used in the preoperative period in some dogs to stabilize their disease prior the surgery. Medical therapy is also of value in dogs in which surgery is not performed. Lastly, medical management is helpful in controlling signs in dogs with metastatic disease. Methods to control

hypoglycemia include frequent feeding, reduced exercise, glucocorticoids, oral hyperglycemic agents, somatostatin analogs, and islet cell cytotoxic drugs. Dogs with recurrent hypoglycemia should be fed a high protein diet that is low in simple sugars and high in complex carbohydrates between 4 and 6 times per day.¹⁰² Such diets are thought to induce less stimulation of tumor produced insulin or at least provide calories at frequent intervals. Prednisone or prednisolone is given twice daily to stimulate gluconeogenesis. Initial dosages should be 0.25 to 0.5 mg/kg/day in divided dosages. This dosage may be increased up to 2 mg/kg/day in refractory cases.

The oral hyperglycemic agent, diazoxide (Proglycem, Schering Corp., Kenilworth, NJ), is helpful in controlling signs of hypoglycemia in as many as 70% of dogs.^{49, 109, 153} The duration of clinical response is reported to be 2 to 15 months with a mean of 6.5 months.⁹² This agent has no antineoplastic effects, rather, it controls hypoglycemia by inhibiting insulin release from tumor cells, by promoting hepatic gluconeogenesis and glycogenolysis through stimulation of the sympathetic nervous system, by decreasing peripheral glucose utilization and by augmenting free fatty acid mobilization.^{49, 102} Recommended dosages are 5 to 30 mg/kg given twice daily. Anorexia, vomiting and diarrhea are the main adverse reactions to diazoxide, decreasing the dosage and giving the drug with meals will reduce these reactions.¹⁰² Combining diazoxide with another thiazide derivative, hydrochlorothiazide (Aldoril), at 2 to 4 mg/kg given twice daily, may potentiate the effects of diazoxide.^{102, 153}

The somatostatin analog, SM 201-945 (Sandostatin or Octreotide), has given subcutaneously to dogs with insulinomas at between 10 to 40 micrograms SQ, two to three times daily. Clinical signs will resolve in some, but not all dogs given this drug.¹⁶⁴ Somatostatin is a potent inhibitor of growth hormone, insulin, glucagon and gastrin. This drug holds promise for future alternative methods of managing this disease. The drug efficacy depends on receptors being present on the tumor surface for this compound and they are not always present, leading to no response. In addition, some dogs become refractory to its effects with time.

Alloxan, a drug toxic to both islet cells and renal tubular epithelium has been tried in a limited number of dogs with metastatic insulinomas.⁵¹ When given as a single intravenous injection to 5 dogs at 65 mg/kg, 4 of 5 became hyperglycemic in 3 to 5 days. Hyperglycemia persisted for several months in 2 dogs and in the other 2, prolonged euglycemia developed. Renal failure is a

significant complication and may develop in approximately 10% of dogs given this drug. Further evaluation of this agent is warranted.

Streptozotocin, a drug with antineoplastic activity against islet cells, has been used in 2 cases of metastatic insulinomas in dogs.^{93, 94} It was highly nephrotoxic in these two animals, and further investigations are needed before it can be recommended for clinical use in the dog. Recently, a modified protocol utilizing aggressive diuresis pre and post-therapy has resulted in fewer instances of renal failure and improved control of malignant insulinomas.

The current protocol for treating metastatic insulinomas with streptozotocin is to diuresis the patient before, during and after administration of the drug to reduce the nephrotoxicity of this agent. Animals are given 18 ml/kg/hr of IV saline. This is done for 3 hours prior to drug administration, during a two hour drug administration, and for 2 hours post administration. Streptozotocin is administered at 500 mg/m² IV over 2 hours along with the saline. Currently, the drug is given once every three weeks for a total of 5 treatments, unless diabetes develops before hand. Butorphenol is given at 0.4 mg/kg SQ just as the drug is given to decrease GI discomfort. Prior to each drug administration, blood work is taken to assess renal function and blood glucose concentrations and therapy given if appropriate. Currently, 15-25% of dogs given this protocol have become diabetic. One dog with mild cardiac disease became fluid overloaded and died of congestive heart failure.

The prognosis for dogs with functional islet cell tumors is highly variable, but generally poor. Surgical cures of insulinomas are not expected. If patients are monitored post-operatively for evidence of recurrent hypoglycemia, it invariably develops. In some cases, a second or third surgery to remove metastatic tumors after signs reoccur may allow further significant disease free time for the animal. Prognostic factors associated with decreased survival times are age at the time of diagnosis (younger dogs have shorter survival times), high pre-operative serum insulin concentrations, and the presence of distant metastases identified at surgery.²² If the tumor is confined to the pancreas (stage-1), survival is significantly longer than dogs in stage 2 (regional node involvement) or stage 3 (regional node and distant metastases). Mean survival times for dogs that are euglycemic after surgery varies from 11 to 17 months.^{22, 23, 24, 49, 73, 78, 92, 139} Although dogs in which hypoglycemia persists post-operatively generally have short term survival, combinations of surgical and

medical therapy have resulted in animals living as long as three and one-half years post-operatively.¹³⁹

Gastrinomas

Functional, non-beta, islet cell pancreatic tumors have been documented for a number of years in man. These tumors produce a syndrome that is characterized by excessive gastric acid production (hyperchlorhydria), peptic esophagitis and gastric and/or duodenal ulceration. This complex of signs, when caused by a gastrin secreting tumor of pancreatic islets, is known as the Zollinger-Ellison syndrome.

There have been nine cases reported which document the existence of pancreatic islet cell tumors that secrete gastrin in dogs and one case in a cat.^{11, 39, 50, 58, 67, 95, 140, 164} Clinical findings have been fairly consistent. Animals range in age from three to nine years and there is no breed or sex predisposition identified. Presenting complaints usually include depression, anorexia, vomiting, diarrhea, and weight loss. Vomiting of blood and/or melena and abdominal pain were observed in 11% of cases.⁵⁰ Laboratory abnormalities include regenerative anemia, neutrophilic leucocytosis, hypoproteinemia, hypoalbuminemia, hypochloremia, hypokalemia, and mild increases in alanine amino transferase and alkaline phosphatase enzymes. Endoscopic abnormalities which may be seen include: erosive esophagitis; gastritis; ulcerations in the esophagus, stomach and duodenum; and gastric mucosal hypertrophy.¹¹ A barium swallow will identify the ulcerations, and prominent gastric mucosal folds. Perforations of the ulcers and regional peritonitis have also been reported. Ultrasound may be useful to identify primary tumors in the pancreas or hepatic metastases.

A definitive diagnosis is based on identifying a pancreatic islet cell neoplasm and documentation of elevated fasting serum gastrin concentrations. Normal fasting serum gastrin concentrations in dogs are reported to be between 20 and 190 picograms/ml and in cats between 28 and 135 picograms/ml.^{11, 50} Serum gastrin concentrations in dogs with gastrinomas have been from 360 to 2,780 picograms/ml and in the one cat, 1,000 picograms/ml.

Most dogs and cats with gastrinomas will be managed by a combination of medical and surgical approaches. Most of these animals are extremely sick when initially evaluated. As such, surgical exploration should be delayed until

patients are stabilized by medical management, except in cases where a perforated gastric or duodenal ulcer exists. Medical management includes supportive care for anemia, fluid, electrolyte, and acid base abnormalities, as well as for ulcer control. Ulcer care usually involves the use of H₂-receptor antagonists such as cimetidine (5 mg/kg 4 to 6 times daily), or ranitidine (2 mg/kg three times daily), and the ulcer protective agent, sucralfate (0.25 gm in cats and 0.5 to 1 gm to dogs, given every 8 hours, 30 minutes prior to H₂ receptor antagonists.¹⁰⁸ Once patients are stabilized, exploratory surgery is recommended. Surgery has the benefits of being both a diagnostic and therapeutic technique and can add valuable prognostic information as well. Gastrinomas are generally small, similar to insulinomas, and surgical removal of primary and metastatic tumors should be attempted. In addition, severe ulcers may be better managed surgically than medically.

The prognosis for animals with gastrinomas is generally poor. Most have had metastatic disease when the diagnosis was first made and have had short term survivals. Early diagnosis would likely improve this situation. In any animal with idiopathic gastric or duodenal ulcers, if serum gastrin concentrations cannot be obtained, an abdominal exploratory is warranted to carefully examine the pancreas for tumors.