Diagnosis and Treatment of Canine Insulinoma

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Insulinoma is an insulin-secreting tumor of the beta cells of the pancreas. It is the most common pancreatic tumor in dogs. Diagnosis of insulinoma can often be difficult due to predominantly unremarkable diagnostic tests, except for hypoglycemia. An amended insulin:glucose ratio and exploratory laparotomy are the most useful tools in diagnosing canine insulinoma. Medical treatment can be used, but is unfortunately only palliative for hypoglycemia. Surgical excision is the most beneficial treatment, however, metastases are usually present at the time of diagnosis. Because these metastases are often microscopic at the time of surgery, prognosis is guarded.

A 7-year-old male castrate Labrador Retriever presented to the Cornell University Hospital For Animals on Friday, May 11, 2001 with a 2-day history of seizures and hypoglycemia. He also had a one-week history of hindlimb weakness and of his hindlimbs occasionally falling out from under him. Two days prior to presentation, the dog had had his first grand mal seizure. The next day (Thursday), he had several more seizures of approximately 1 minute in duration. His owners brought the dog to the local veterinarian who documented a blood glucose level of 30 mg/dl (normal range 60-120 mg/dl). The local veterinarian started an intravenous infusion of dextrose to treat the hypoglycemia, but the dog s blood glucose levels continued to be variable and seizure activity continued throughout the night. On Friday, May 11, 2001, the labrador was brought to Cornell for further evaluation.

On presentation, the dog seemed slightly agitated, nervous, and hyperexcited. Physical examination was within normal limits except for a II/VI systolic heart murmur, weak femoral pulses, and small petecchiation on his ventral abdomen. A complete blood count and coagulation panel were submitted; both were within normal limits. A chemistry panel was submitted and revealed a slight hypernatremia (153 mEq/L; normal 142-151) and slight hyperchloremia (120 mEq/L; normal 107-117), a slight increase in AST activity (69 U/L, normal 16-50), and a 2.5-fold increase in CK activity (621 U/L; normal 58-241). Blood glucose level on presentation was low normal (64 mg/dL; normal 60-120). Systolic blood pressure (170 mmHg) and the oxygen saturation of his blood (95%) were both within normal limits. An abdominal ultrasound was performed revealing no significant abnormalities. The dog was admitted to the hospital and intravenous fluid therapy supplemented with dextrose was initiated.

During the night, the dog s blood glucose level dropped to 48.3 mg/dL and he remained hypoglycemic, despite supplementation, until the next morning. Also during the night, he began hypersalivating and lip-smacking and became very anxious. A dose of Valium was administered and the signs abated and the dog became more aware. However, similar signs recurred several times and began to progress to include flank-biting, head tremors and muscle fasciculations. At this point, he also became hyperthermic (106° F). Phenobarbital therapy was initiated to help control his seizure activity. When the Phenobarbital did not adequately control his seizures, it was presumed that his prolonged seizure activity had produced a seizure focus in his brain. Because of this, a constant rate infusion of pentobarbital was initiated to keep the dog in a low plane of anesthesia to completely control his seizures and prevent further damage.

Because the dog s primary signs were seizures and hypoglycemia, an insulinoma was high on the differential diagnosis list. To aid in the diagnosis, blood insulin levels and simultaneous blood glucose levels were taken. An amended insulin:glucose ratio was calculated and was highly suggestive of an insulinoma. Therefore, the dog had exploratory surgery on May 16, 2007. A mass was found on the pancreas, removed, and submitted for histopathology. The histopathology described the mass as an islet cell carcinoma, confirming the presumptive diagnosis of insulinoma.

An insulinoma is an insulin-secreting tumor of the beta cells of the pancreas. It is the most common pancreatic tumor in dogs.[1] The excess insulin secreted by the neoplastic beta cells decreases blood glucose levels. Clinical signs are primarily related to the associated hypoglycemia. Clinical signs of hypoglycemia often occur episodically, provoked by feeding, fasting, or exercise. Neurological signs predominate because glucose is the primary fuel used by the central nervous system. These signs can include seizures, weakness, lethargy, ataxia, posterior paresis, bizarre behavior, mental dullness, confusion, and potentially, coma. If the blood glucose drops rapidly enough, sympathetic tone can increase, causing catecholamine release and adrenergic signs. These sympathoadrenal signs can include tremors, muscle fasciculations, nervousness, irritability, or intense hunger. In a clinical situation, to confirm that low blood glucose levels cause the observed signs, one can attempt to fulfill Whipple s Triad. Whipple s Triad is a set of three criteria to determine that clinical signs are due to hypoglycemia:

1) Neuromuscular signs must be seen with fasting or exercise.

2) Low blood glucose levels must be associated with the clinical signs.

3) A reversal of clinical signs occurs with administration of glucose.[2,3]

This set of criteria can be very helpful when trying to prioritize clinical signs and associated differential diagnoses. Differential diagnoses for hypoglycemia include hypopituitarism, hypoadrenocorticism, hepatic failure, glycogen storage diseases, extrapancreatic neoplasia, sepsis, insulinoma, puppy hypoglycemia, pregnancy hypoglycemia, starvation, insulin overdosage and lab error. The last five differentials can often easily be ruled out by signalment and history.

Seizures are the most common clinical sign associated with insulinomas.[2,4,5,6] A seizure is a clinical manifestation of an excessive discharge of hyperexcitable cerebrocortical neurons with loss of consciousness, generalized muscle activity, excessive salivation, jaw chomping, limb paddling and often urination or defecation.[7] Seizures are typically grouped into generalized or partial seizures. Generalized seizures have general cerebral involvement, generalized muscle activity (facial twitching, jaw chomping, limb paddling, etc.), salivation, micturition, defecation, and a loss of consciousness. On the other hand, partial seizures have a focal onset in one cerebral hemisphere and usually have unilateral motor signs (unilateral facial twitch, tonic movement of one limb, etc). Partial seizures can also manifest as behavioral changes and can be with or without a loss of consciousness. When evaluating seizures, it is also important to differentiate between seizure-like disorders and true seizures. Syncope is a transient loss of consciousness from insufficient delivery of oxygen or glucose to the brain.[7] It is an initial collapse with loss of consiousness that can be followed by generalized motor activity, which can often be confused with a seizure. Differential diagnoses for seizures are generally split into two categories: intracranial causes and extracranial causes. Intracranial causes include neoplasia, vascular changes such as

ischemia or hemorrhage, inflammatory causes (infectious or immune-mediated), trauma, congenital malformations, and acquired epilepsy. The extracranial category includes metabolic causes, such as hepatic encephalopathy and insulinoma, and toxic causes, such as lead, organophosphates or ethylene glycol. Another important cause of seizures, that does not quite fit in either the intra- or extra-cranial categories, is idiopathic epilepsy.

The diagnosis of insulinoma is often difficult. Most routine labwork is unremarkable. Complete blood count, chemistry panel, and urinalysis are usually within normal limits except for hypoglycemia. Radiographs are unrewarding. Abdominal ultrasound has mixed results. Ultrasonography can be useful in detecting pancreatic tumors, however, a negative ultrasound does not rule out insulinoma.[2,6,8] Computerized tonography (CT) has similar results to ultrasonography; it can be useful, but a negative test does not rule out insulinoma. Blood insulin levels can be obtained, but are not very helpful alone. Insulin levels are most useful with simultaneous blood glucose levels. In a normal animal, hypoglycemia causes suppression of insulin secretion. Low blood glucose levels do not affect insulin secretion by neoplastic cells. Therefore, the relationship between insulin and blood glucose can be very helpful in diagnosing insulinoma. An Amended Insulin:Glucose Ratio can evaluate this relationship. The Amended Insulin:Glucose Ratio (AIGR) is calculated with the following formula:

$$\frac{\text{Insulin} \times 100}{\text{Blood glucose} - 30}$$

An AIGR of greater than 30 suggests an insulinoma.[2,4,9] While the above diagnostics can be useful, exploratory surgery is the most helpful and definitive diagnostic tool. Exploratory surgery also allows for treatment, or removal of any tumors and metastases that are observed.

The treatment of insulinoma can be medical or surgical. The goal of medical therapy is to reduce the frequency and severity of clinical signs and to prevent acute hypoglycemic crisis.[2,3,6,9] Medical treatment is really only palliative for hypoglycemia. The first method of medical management is to manipulate the diet. Small frequent feedings can help to maintain consistent blood glucose levels and decrease the likelihood of a hypoglycemic crisis.[2,3,5,9] A diet with high protein, moderate fat, and moderate complex carbohydrates (avoid simple carbohydrates) can also be helpful.[2,3,9] Glucocorticoids are used to increase blood glucose levels. They stimulate hepatic glycogenolysis and gluconeogenesis. interfere with cell receptors for insulin and decrease cellular use of glucose.[2,3,9] If dietary management and glucocorticoids are not effective, diazoxide can be used. Diazoxide, a nondiuretic benzothiadiazide, inhibits secretion of insulin by decreasing intracellular release of Ca++ and blocking the release of insulin granules. It also stimulates hepatic glycogenolysis and gluconeogenesis and inhibits the use of glucose by stimulating the adrenergic nervous system and secretion of epinephrine.[2,3,5,9] However, diazoxide does not inhibit insulin synthesis and does not have any antineoplastic effects.[2,3] Somatostatin, a product normally produced by the D cells of the pancreas, inhibits the synthesis and secretion of insulin by normal and neoplastic beta cells. However, the response to somatostatin therapy is variable.[2] Streptozotocin, an alkylating chemotherapeutic, is finding renewed use in the treatment of insulinoma. When initially used, nephrotoxicity was a severe complication. Recent changes in administration have decreased the nephrotoxic affects. Streptozotocin is selectively toxic to pancreatic beta cells. It inhibits the production and secretion of

insulin by removing pyridine nucleotides and decreasing the uptake of pyridine nucleotide precursors.[2,9,10]

The goal of surgical treatment is to remove all abnormal tissue and look for metastases. Fortunately, most pancreatic masses are easily visible or palpable.[2,4,5] Pre-operatively, medical therapy is used to prevent episodes of severe hypoglycemia and to maintain adequate blood glucose levels. Often medical therapy is used to stabilize a patient before undergoing surgery. During surgery, fluid therapy with dextrose should be used and the blood glucose levels should be monitored every 30-60 minutes. The entire abdomen should be thoroughly examined for metastases, most commonly found in the liver and regional lymph nodes. Gentle manipulation of the pancreas is crucial. Because of the sensitivity of pancreatic tissue, pancreatitis is a very common postoperative complication.[2,3,6] Prophylactic treatment of pancreatitis is often beneficial. Hyperglycemia is another potential postoperative complication. Dogs often develop diabetes mellitus after surgery, presumably from inadequate insulin secretion from normal beta cells that have atrophied in the presence of the insulinoma.[2,3] This hyperglycemia may be transient or long—term and may need to be treated with insulin. Hypoglycemia can also occur as a postoperative complication. In this case, hypoglycemia is usually due to metastases and medical therapy should be initiated to prevent clinical signs of hypoglycemia and acute hypoglycemic crisis.

The prognosis for dogs with insulinoma is guarded, regardless of treatment. Canine insulinoma is considered a malignant neoplasia, with metastases usually present by the time of diagnosis. With medical treatment only, the median survival time is about 70-80 days.[6] Surgery significantly lengthens the median survival time to about 350

days.[6] If hypoglycemia recurs after surgery, medical management should be initiated to reduce clinical signs of hypoglycemia and avoid hypoglycemic crisis.[3,4,5,9] This may increase survival time in some cases.

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