Weakness & Collapse in a Beagle

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Blue, a 10-year-old spayed female beagle, presented to the University of California William Prichard Veterinary Teaching Hospital to be evaluated for a 4-month history of episodic weakness and collapse.

HISTORY
The owner noted that Blue was lethargic and experiencing short episodes of weakness and collapse. No seizures or unconsciousness had been noted. The time between episodes of weakness and collapse was variable, ranging from weekly to once every 3 to 4 weeks. Blue would no longer go on walks further than a mile.

No change in water consumption, appetite, urination, or defecation had been noted. Blue’s food consisted of a senior dry kibble fed twice daily along with several treats per day; she had not had any incidences of vomiting or diarrhea. Blue was not currently receiving any medications.

PHYSICAL EXAMINATION
Blue was obese with a body condition score of 8 out of 9. Vitals were within normal limits. There were no murmurs or arrhythmias, masses or organomegaly, or muscle atrophy. Peripheral lymph nodes were < 1 cm.

LABORATORY ANALYSIS
The initial laboratory evaluation consisted of a CBC, serum biochemical profile, and urinalysis. The CBC and urinalysis were unremarkable. Serum biochemical profile results included (Table 1, page 54):

- Mild increase in hepatocellular enzymes—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- Normal alkaline phosphatase (ALP)
- Marked hypoglycemia.

DIFFERENTIAL DIAGNOSIS
Based on history, signalment, and physical examination (including body condition), the primary differential diagnoses for hypoglycemia and episodic weakness (Table 2, page 54) in this dog included:

- Insulin-secreting beta-cell tumor (insulinoma)
- Extrapancreatic neoplasia (eg, hepatoma, leiomyoma, leiomyosarcoma, lymphosarcoma, etc)
- Atypical hypoadrenocorticism (Addison’s disease).
Consider This Case

## ADDITIONAL DIAGNOSTICS

### Serum Insulin Concentration
Serum insulin concentration, from the blood sample demonstrating hypoglycemia (35 mg/dL), was significantly increased (> 310 mcU/mL; reference interval, 5–20 mcU/mL) and consistent with a diagnosis of an insulin-secreting beta-cell tumor.

### Diagnostic Imaging
Thoracic radiographs were taken to determine if metastatic lesions were present; there were no significant abnormalities.

Abdominal ultrasound revealed a markedly enlarged (1.5 cm) mesenteric lymph node in the right cranial abdomen near the caudal vena cava, which was consistent with a metastatic lesion, and a 0.5-cm hypoechoic nodule in the liver, which could represent metastatic disease or benign change. No definitive pancreatic nodules were identified (Figure 1).

Computed tomography (CT) was not performed.

### SURGICAL TREATMENT
Surgical exploration of the abdomen found nodules in the right and left limbs of the pancreas. The nodule in the right limb was resected and the majority of the left limb of the pancreas was removed (Figure 2). Several mesenteric lymph nodes were enlarged and also removed (Figure 3).

### Histopathology
Histopathology confirmed:
- Infiltrative beta cell carcinoma in the left limb of the pancreas (Figures 4 and 5)
- Metastatic beta cell carcinoma in the mesenteric lymph nodes.

Neoplastic cells in both the pancreas and mesenteric lymph node were strongly immunoreactive to antibodies against insulin, confirming insulin-secreting beta-cell carcinoma (Figure 6). No evidence of neoplasia was noted in the right limb of the pancreas or the hepatic biopsy.

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### TABLE 1. PERTINENT SERUM BIOCHEMICAL PROFILE RESULTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>130</td>
<td>21–170</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>96</td>
<td>19–67</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>87</td>
<td>19–42</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>35</td>
<td>70–138</td>
</tr>
</tbody>
</table>

### TABLE 2. DIFFERENTIAL DIAGNOSES FOR EPISODIC WEAKNESS & HYPOGLYCEMIA

#### Episodic Weakness
- Cardiovascular: Arrhythmias
- Endocrine: Hypoadrenocorticism, pheochromocytoma
- Metabolic: Hypocalcemia, hypoglycemia, hypokalemia
- Neuromuscular: Myasthenia gravis

#### Hypoglycemia
- Drug-associated/iatrogenic
  - Ethylene glycol toxicity
  - Insulin therapy
  - Oral hypoglycemics
  - Sulfonylurea therapy
  - Xylitol toxicity
- Extrapancreatic neoplasia; examples include:
  - Carcinoma (mammary, salivary, pulmonary)
  - Hepatocellular carcinoma, hepatoma
  - Leiomyoma, leiomyosarcoma
  - Leukemia
  - Lymphosarcoma
  - Melanoma
  - Plasmacytoma
- Hepatic enzyme deficiencies
  - Cori’s disease (Type II glycogen storage disease)
  - Von Gierke’s disease (Type I glycogen storage disease)
- Hepatic insufficiency
  - Chronic fibrosis, cirrhosis
  - Hepatic failure
  - Portacaval vascular anomaly and portal vein hypoplasia
- Hypoadrenocorticism (Addison’s disease)
- Hypopituitarism
- Idiopathic hypoglycemia
  - Hunting dog hypoglycemia
  - Neonatal/juvenile hypoglycemia (especially toy breeds)
  - Postparturient hypoglycemia
- Insulin-secreting beta-cell tumor (insulinoma)
- Polycythemia (severe)
- Sepsis
  - Septic peritonitis, pyothorax, pyometra, urosepsis, etc
  - Severe canine babesiosis (rare)
- Starvation (prolonged)
- Spurious/artifact
  - Portable blood glucose meters
  - Serum separation (prolonged storage of blood)
Figure 1. This ultrasound image depicts a markedly enlarged and hypoechoic lymph node, suspected to represent metastatic neoplasia, in the right cranial abdomen, measuring approximately 1.35 cm in width. A definitive pancreatic nodule could not be identified.

Figure 2. Gross pathology image of an infiltrative well-demarcated mass within the left limb of the pancreas.

Figure 3. A well-demarcated mass (arrows) effaces the lymph node parenchyma expanding the capsule. The uniform neoplastic cells are arranged in packets and anastomosing cords are defined with fine fibrovascular stroma. Small cords of neoplastic cells extend into the subcapsular lymphatics.

Figure 4. Histopathology of a section of pancreas showing a densely cellular, well demarcated, and variably encapsulated mass (light pink) that compresses the pancreatic parenchyma and extends into the lymphatics. (Magnification, 2×)

Figure 5. Histopathology of a section of pancreas: this mass is composed of uniform neoplastic cells arranged in packets (large arrow) and anastomosing cords defined with fine fibrovascular stroma (small arrow). The cells have round nuclei with coarsely stippled chromatin and 1 to 2 small nucleoli. (Magnification, 40×)

Figure 6. Immunohistochemistry reveals neoplastic cells within the pancreas that are strongly immunoreactive against insulin (large arrow), confirming an insulin-secreting beta-cell tumor. Beta-cell islets throughout the normal pancreas (small arrow) are also immunoreactive against insulin. (Magnification, 2×)
INSULINOMA TREATMENT: WHAT ARE YOUR OPTIONS?

MEDICAL VERSUS SURGICAL
Medical therapy is an option for treatment of insulinoma, but surgery potentially provides palliation with a resectable mass. If metastatic disease is noted, surgical cytoreduction results in improved clinical signs and significantly longer survival than medical therapy alone.1,2,5

SURGICAL COMPLICATIONS
Postoperative acute pancreatitis is the main complication associated with surgical manipulation of the pancreas. Other possible sequelae after surgery include persistent hypoglycemia due to metastatic disease and development of diabetes mellitus due to beta cell atrophy.1,5

MEDICAL MANAGEMENT
Medical management is the treatment of choice when celiotomy is not an option due to metastatic disease, inoperable neoplasia, concurrent disease, or financial restraints. This management includes:
- Dietary therapy
- Limited strenuous exercise
- Glucocorticoids for insulin antagonism
- Diazoxide to inhibit insulin secretion and stimulate hepatic gluconeogenesis.

Dietary therapy involves feeding multiple small meals (3 to 6 feedings per day) of a high-fiber food that has decreased simple carbohydrate and sugar content. There are no studies that evaluate the efficacy of various diet properties in dogs with islet cell tumors. The goal of dietary therapy is to supply a constant supply of glucose to counter the excess insulin produced by the tumor. Therefore, frequent meals, diets with fiber, and avoidance of simple sugars has worked well in our experience.

Glucocorticoid therapy should be administered when dietary therapy is no longer effective at preventing signs of hypoglycemia. Glucocorticoids antagonize the effects of insulin at a cellular level and stimulate hepatic glycogenolysis. Prednisone is usually initiated at 0.25 mg/kg Q 12 H, and the dose increased as needed to control clinical signs (NOT to attain euglycemia).5,7

Other therapies allow reduction in glucocorticoid dose. Diazoxide therapy, when available, may be pursued if clinical signs of hypoglycemia persist or severe clinical signs of hypercortisolism develop.1,2,5,8 Diazoxide, a nondiuretic thiazide, inhibits insulin secretion and tissue use of glucose, while stimulating gluconeogenesis. It does not inhibit insulin synthesis or have cytotoxic (antineoplastic) effects. Initial dosage of 5 mg/kg PO Q 12 H, not to exceed 60 mg/kg/day; this dose can then be increased as needed to minimize clinical signs of hypoglycemia.

PROGNOSIS
Long-term prognosis is poor to guarded given the high likelihood of metastatic lesions at the time of diagnosis. Survival depends on the owner’s willingness to pursue aggressive treatment. Studies have documented significantly longer survival times in animals treated with surgery and medical therapy compared to those treated with medical therapy alone.1,5 Relapse following partial pancreatectomy (recurrence of hypoglycemia) should prompt initiation of medical therapy. One study documented a median survival time of 1316 days in dogs that had undergone surgery followed by medical therapy when metastatic disease occurred.7

[Image of a dog eating from a bowl]
Post Operative Recovery
Blue recovered from anesthesia without complications. Blood glucose measurements stabilized at 70 to 100 mg/dL while in the hospital post operatively. No specific medical therapy was started postoperatively except for routine postoperative care, including IV fluids, pain medication, antiemetics, and small frequent meals of a low-fat diet.

FOLLOW-UP
Blue was discharged 4 days after surgery. She was initially fed a low-fat food (to reduce risk of pancreatitis post operatively) three times a day until the 1-month recheck. A follow-up was recommended in 10 to 14 days for suture removal and to recheck her blood glucose.

Two-Week Recheck
At the 14-day recheck, Blue’s incision had healed nicely and blood glucose measurements were 66 and 71 mg/dL.

One-Month Recheck
At the 1-month recheck, Blue’s blood glucose, which was measured at home, ranged from 50 to 80 mg/dL, with occasional signs compatible with hypoglycemia. The owners noted that Blue had improved significantly since surgery, but recurrence of clinical signs with concurrent low blood glucose measurements confirmed metastatic disease containing functional islet cells that were probably producing insulin.

Blue’s food was switched to a diet with a moderate fat content, a mix of insoluble and soluble fiber, and limited simple sugars; she was fed 4 times a day.

Four-Month Recheck
At the 4-month recheck, most of Blue’s blood glucose measurements were approximately 50 mg/dL; however, her measurements were 70 to 80 mg/dL in the evenings. Blue was prescribed prednisone, 2.5 mg (0.16 mg/kg) PO Q 12 H, and fed 4 meals a day.

(continued next page)

WHAT YOU NEED TO KNOW ABOUT BETA CELL TUMORS
- **Definition**: A functional beta-cell tumor (insulinoma) develops from the pancreatic islets and secretes insulin independent of suppressive effects of hypoglycemia.
- **Predilection**: Most tumors occur in middle-age to older dogs; many dogs demonstrate clinical signs for 1 to 6 months prior to presentation.
- **Clinical Signs**: Primary clinical signs are associated with neuroglycopenia and include seizures, weakness, collapse, mental dullness, and tremors. Clinical signs are often short in duration and episodic. Rarely, a hypoglycemic neuropathy can occur.
- **Initial Diagnostics**: Diagnosis is based on demonstrating hypoglycemia and concurrent hyperinsulinemia. When blood glucose is < 50 mg/dL, serum insulin concentration should be evaluated in collected samples.
- **Imaging**: Failure to identify a mass with advanced imaging (ultrasound, CT) does not rule out a beta-cell tumor.
- **Definitive Diagnosis**: Definitive diagnosis is confirmed by histopathology with special hormone immunohistochemistry.
- **Additional Diagnostics**: If blood glucose is > 60 mg/dL but insulinoma is suspected based on clinical signs, consider repeat measurement of blood glucose during fasting while under close observation.
- **Malignancy**: Virtually all beta-cell tumors are malignant in dogs; 40% to 50% have visible metastatic disease at surgery. Metastatic spread is usually to local lymph nodes, lymphatics, and liver.
- **Surgical Treatment**: Treatment of choice is surgical resection; it has been shown to increase survival time even if complete excision is not possible.
- **Medical Treatment**: Medical treatment is aimed at controlling clinical signs of hypoglycemia and includes frequent meals, avoiding strenuous exercise, and low-dose prednisone (initially, 0.25 mg/kg PO Q 12 H). Diazoxide, when available, can also be administered (5 mg/kg PO Q 12 H) for management of hypoglycemia.

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OUTCOME
Blue was last evaluated 21 months following surgery. She had measured blood glucose concentrations of 50 to 80 mg/dL and was being maintained on prednisone (2.5 mg PO Q 12 H), with minimal hypoglycemic complications.

ALP = alkaline phosphatase
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CT = computed tomography

References