Easy's Low Ride

by

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Introduction:

Insulinomas are functional tumors of β-cells of the islets of Langerhans of the pancreas. These tumors secrete insulin, even in the face of hypoglycemia.[1,3,4,9] Insulinomas can be referred to as pancreatic β-cell tumors, adenomas, or adenocarcinomas of the pancreatic islet cells.[9] Insulinomas are the most common pancreatic neuroendocrine tumor in dogs and are malignant, unlike in humans where insulinomas are considered benign in nature.[2,3,9] Clinical signs result from hypoglycemia, these signs can be vague but weakness, changes in mentation or behavior, and seizures are considered the most common signs.[1,2,3,14] No breed or sex predisposition has been noted but typically medium to large breed dogs of middle to older age are more commonly affected.[9] Affected animals physical exams are generally unremarkable aside from the effects of hypoglycemia.[3,14,18] Insulinomas are considered uncommon in dogs, rare in cats, but is fairly common in ferrets.[18]

Historically, the diagnosis of insulinoma depended on demonstrating the features of the Whipple's triad. Whipple's triad consist of clinical signs associated with hypoglycemia, fasting blood glucose concentration less than or equal to 40 mg/dL, and relief of neurological signs with feeding or administering glucose.[3,9] While diagnosis of insulinomas has evolved over the years, definitive diagnosis can only confirmed by histology.[4] A tentative diagnosis can be made and supported by a variety of tests such as fasted blood glucose, insulin-to-glucose ratio, serum fructosamine, and multiple imaging modalities.[3,9,4,15] As with any diagnostic testing, all should be interpreted with current clinical signs in mind and knowledge of each tests weaknesses.[3] Evidence for metastasis is commonly investigated through radiographs, ultrasonography, and computed tomography. Insulinomas can be staged as (Stage I) confined to the pancreas, (Stage II) metastasis of regional lymph nodes, or (Stage III) distant metastasis is present.[1,4,16]

Generally, surgical therapy is considered the treatment of choice for insulinoma patients with studies showing longer median survival times.[1,20] Medical management can be implemented for those who are not good surgical candidates, those that experience persistent hypoglycemia after surgery, or in cases when owner does not elect for surgery.[3,4]

History and Presentation:

An 8-year-old male neutered mixed breed dog presented to Mississippi State University College of Veterinary Medicine Emergency Department for seizures that had occurred that day. The patient had been experiencing seizures for the past 4 months, about 1 seizure per day every 10 days. The patient had been previously prescribed phenobarbital by his primary, but the seizures persisted, and he had not received any within the past month. Earlier in the day, the patient had 3 seizures before seeing his primary veterinarian. At the primary veterinarian, the patient had another seizure. The patient's blood glucose was low at 42 mg/dL and he was administered a dextrose bolus which brought his blood glucose up to 134 mg/dL. The patient was then referred for suspect insulinoma or xylitol toxicity.

On presentation to MSU-CVM ER, the patient weighed 37 kg with a body condition score of 8/9. His temperature was 102.1˚F. His heart auscultated with a rate of 96 beats per minute and no murmurs or arrhythmias were detected. His lungs auscultated normally with no crackles or wheezes, and he was panting. His hydration appeared to be normal with pink, moist mucous membranes. His capillary refill time was less than 2-3 seconds indicating adequate perfusion. His abdomen palpated smooth and nonpainful. His eyes were clear and free of discharge. His left upper canine was missing and there seemed to be a mass in the gum line where the canine would be. His ears contained a mild amount of debris bilaterally. His lymph nodes palpated smooth and symmetrical bilaterally.

The patient was admitted to MSU-CVM for further work-up with the internal medicine department. After bloodwork and imaging, a presumptive diagnosis of insulinoma was made. The serum insulin- glucose levels had still not returned but on 4/5/21, the patient was discharged with instructions to monitor the patient for hypoglycemic episodes and feed small frequent meals to stabilize his blood glucose. The serum insulin – glucose ratio came back on 5/9/21, supportive of the diagnosis and an appointment with the MSU-CVM surgery department.

On April 13th, upon presentation to MSU-CVM surgery department, his physical exam was unchanged from his prior visit and his vitals were within normal limits. Since his last visit at MSU-CVM, the patient had not experienced any seizures. On presentation, he did have muscle fasciculations in his hind legs and a blood glucose was taken reading 24 mg/dL.

Diagnostic Approach:

The following diagnostics were performed by the emergency department. Following the initial physical exam, a limited neurological exam was within normal limits (no CP deficits, normal palpebral, PLR, menace, and no nystagmus noted). Thoracic FAST scan was performed with no abnormalities noted but an abdominal FAST scan showed an enlarged spleen. Blood pressure readings ranged from, 227/132 (162) to 170/70 (104) to 153/63 (93) mm Hg, consistent with hypertension. The patient was oxygenating well with a pulse ox of 96%. His blood glucose was evaluated and was low at 64 mg/dL. Karo syrup was administered orally, and twenty minutes later his blood glucose was 37mg/dL. Blood was submitted for a CBC, chemistry panel, and serum insulin - glucose ratio. CBC abnormalities included lymphopenia (Lymph % 9.0 [reference range: 10.1 - 48.0]); (Lymph 680.4 /ul [reference range: 1,100.0 – 4,800.0]), and thrombocytopenia (141 x 10^3 /ul [no reference range listed]), however it was reported that the platelet estimate appeared adequate with 161 estimated platelets with rare megaplatelets, slight

polkilocytosis (rare), slight echinocytes/creneated RBC. Chemistry abnormalities included hypoglycemia (Glucose 37 mg/dL [reference range: 75-125 mg/dL]); elevated liver enzyme (ALP 205 U/L [reference range: 10-90 U/L]); increased creatinine kinase (CK 921 U/L [reference range: 50-300 U/L]). The serum insulin – glucose ratio was sent out to Michigan State University. Due to the patient's status upon presentation, physical exam, and bloodwork, differential diagnoses at this time were insulinoma, toxin ingestion, and other neoplasms. An intravenous catheter was placed, and he was hospitalized overnight. The patient was fed small meals every four hours and he was placed on seizure watch in the intensive care unit.

Thoracic radiographs were taken the same day as presentation for a pulmonary metastasis check. Radiographs revealed a mild and diffuse bronchial pulmonary pattern consistent with age related change, or chronic bronchitis if clinically suggestive. There was no evidence of pulmonary metastasis. Abdominal radiographs were also performed showing an incompletely evaluated soft tissue opaque mass with a convex margin that was seen on both the ventrodorsal and lateral projections in the craniodorsal abdomen that measures 7x4 cm. This mass like structure was likely due to superimposition of normal structures and concurrent splenomegaly however, neoplasia or granuloma formation could not be ruled out at that time. There was also mild splenomegaly possibly from extramedullary hematopoiesis, lymphoid hyperplasia, or neoplasia. At this point in the diagnostic work up, a contrast enhanced computed tomography of the abdomen was recommended for further evaluation of a suspected insulinoma.

The patient was transferred from ER and the following diagnostics were performed by the internal medicine department. A baseline cortisol was ordered and determined to be within normal limits (Cortisol, Baseline 2.6 ug/dL [reference range: 0.5- 6.0]). The owner elected for abdominal ultrasound to possibly confirm the presence of a mass. Ultrasound revealed a

moderate amount of hyperechoic material within the gallbladder lumen most likely due to cholestasis. At the left limb of the pancreas, an irregularly shaped, irregularly marginated, heterogeneously hypoechoic mass measured 2 cm in thickness without color flow on doppler interrogation. The primary differential is pancreatic neoplasia such as the suspected insulinoma.

The patient was discharged with instructions to feed small frequent meals every 4-6 hours to prevent low blood sugar as well as monitor him for signs of hypoglycemia. The serum insulin - glucose ratio levels returned from the lab on April 9th showing, (Insulin, fasting RIA 24.2 ulU/mL [reference range: 8.1-31.9]); (Glucose, fasting hexokinase 33 mg/dL [reference range: 81-118]); (Ratio, fasting calculated 0.73 I:G Ratio [reference range: 0.11 – 0.33]). The high I:G ratio demonstrated high insulin levels in the face of hypoglycemia, supporting the diagnosis for insulinoma.

On April 13th, the patient presented to the MSU-CVM surgery department and was admitted into the ICU for blood glucose monitoring and seizure watch until his surgery on April 14th.

Pathophysiology:

The pancreas is composed of both the exocrine pancreas and the endocrine pancreas. The right limb of the pancreas lies within the mesoduodenum and is drained by the pancreatic duct which is the main duct in cats. The left limb lies within the deep leaf of the greater omentum and is drained by the accessory pancreatic duct which is the main duct in dogs.[9] The exocrine pancreas is responsible for digestive enzymes that are secreted into the duodenum by the pancreatic ducts. The endocrine pancreas is composed of β-islet cells that are insulin producing,

α- cells that produce glucagon, δ cells which secrete somatostatin, and pancreatic polypeptide-producing cells. Insulinomas are functional tumors of β-cells of the islets of Langerhans. These tumors secrete insulin despite the presence of hypoglycemia.[2,3,4,9] In normal, healthy animals, the blood glucose is maintained within a range of 70mg/dL to 110mg/dL. If the blood glucose rises above the higher range, the β-cells secrete insulin. If the blood glucose drops below the range, insulin production and secretion is halted to prevent further drops in blood glucose. Subsequently, in hypoglycemic states, the body is also signaled to increase secretion of glucagon resulting in increased glucose production from hepatic cells. With insulinomas, the normal feedback mechanisms are no longer working and neoplastic β-cells are able to synthesize and secrete insulin regardless of hypoglycemia.[3,4,9,11] Insulin has many roles with the main being facilitation of uptake, storage, and use of glucose by the liver, muscle, and adipose tissue.[3] Glucose is derived from digestion of carbohydrates, breakdown of glycogen, and synthesized mainly by the liver and kidneys. Gluconeogenesis is the synthesis of glucose which is performed by the liver, intestines, and kidneys. One of insulins functions include the inhibition of gluconeogenesis. [5,6,17] While all cells and tissues are affected by hypoglycemia, the brain is dependent upon a constant blood glucose concentration in order to function and is not capable of gluconeogenesis nor glycogen storage.[3,6,8,11,17] This makes the brain extremely vulnerable to hypoglycemia and creates a state known as neuroglycopenia.[3,5,6,17] This state leads to clinical signs of hypoglycemia such as weakness, ataxia, muscle fasciculations, and seizures.[3] Studies have shown that prolonged episodes of neuroglycopenia can lead to permanent changes.[11,16]

Treatment:

On April 14th, 2021 the patient underwent a partial pancreatectomy. Under general anesthesia, the patient was clipped, aseptically prepared, placed in dorsal recumbency. An

incision was made through the skin along ventral abdominal midline from the xyphoid bone to several centimeters caudal to the umbilicus. Once inside the abdomen, no abnormalities were appreciated aside from the known pancreatic mass in the proximal left limb of the pancreas, with extension of the mass towards the mesentery. The pancreas was examined using a combination of gentle palpation and visual inspection. The insulinoma was visualized in the left limb of the pancreas. The omental leaf overlying the left limb of the pancreas was bluntly separated to allow direct visualization of the entire pancreas. The insulinoma and associated left limb of the pancreas were excised using blunt dissection with curved Mosquito hemostats, Metzenbaum scissors, and ligasure being careful to avoid the cranial and caudal pancreaticoduodenal vessels and the common bile duct. Biopsy of the quadrate liver lobe was taken using the guillotine method, the ileocolic lymph node was biopsied with a wedge method.

The patient's surgery was uneventful. A dysphoric anesthetic recovery was resolved by administration of dexmedetomidine intravenously once. Postoperatively he was maintained on intravenous fluids, trazodone, Tylenol 4, and a fentanyl constant rate infusion. The patient's blood glucose was stable at 76 mg/dL post operatively but later that evening his blood glucose had increased to 312 mg/dL. His blood glucose was checked throughout the night, and it remained high. The next morning on April 15th, the blood glucose was 278 mg/dL. He was given 0.1unit/kg of insulin at 8:30am and at the 10am check his blood glucose was 257 mg/dL. Throughout the day and night the patient was hyperglycemic with the lowest being 192 mg/dL and the high 366 mg/dL the morning of April 16th. After consultation with the internal medicine department, it was decided to maintain the patient on Vetsulin and a free-style libre was placed to monitor his blood glucose. In the days following surgery, the patients' blood glucose was

stabilized with vetsulin, and the patient was no longer dependent upon intravenous fluids or fentanyl for hydration and management.

Case Outcome:

The pancreatic tissue including the mass, lymph node, and liver biopsy were all submitted for histopathologic evaluation. It was noted that the lymph node and liver were reactive, but no neoplastic features were observed. The pancreatic tissue and mass were representative of a malignant neuroendocrine carcinoma. The neoplastic cells had moderate amounts of vacuolated to faintly granulated eosinophilic cytoplasm and a prominent round to oval vesicular nucleus with a single nucleolus. Mitotic figures are common (~7 per 7 high powered fields) in select areas. Neoplastic stroma compressed marginating pancreatic tissue and multifocally dissects into neighboring pancreatic stroma. An insulin IHC stain was submitted and came back strongly labeled neoplastic epithelial cell cytoplasm confirming the diagnosis of insulinoma.

Five days after the patient's procedure, he was discharged to his owner with instructions to limit activity, cold pack his incision, maintain his Elizabethan collar, and administer the oral medications, Tylenol and Trazodone. He also was sent home with a Free style libre for glucose monitoring and instructions to administer vestsulin as needed. On the 29th, he returned to MSU-CVM internal medicine department for a recheck as well as to have his staples removed. At this time his owner reported that he gave insulin once on 4/20/21 but otherwise the patients' blood glucose remained below 200 mg/dL.

Discussion:

The patients presenting signs and history of seizures warranted a workup for common causes of hypoglycemia. In cases of hypoglycemia a list of differential diagnoses should be included such as drugs or toxins, insulinomas, hypoadrenocorticism, neoplasms, malnutrition, and sepsis.[5,6,11] Diagnostically, bloodwork abnormalities seen with insulinomas include hypoglycemia, hypokalemia, and elevated liver enyzmes.[3,18] Radiographs of the thorax and abdomen should be obtained to rule out pulmonary metastasis or any visible masses. Historically, insulinomas will metastasize to the regional lymph nodes and liver before lung, but pulmonary metastasis is still reported.[4,18] Many authors state that the detection of insulinomas with ultrasonography is highly variable and dependent upon the ultra-sonographer. Insulinomas are described to be hypoechoic nodules or masses. [19] One study showed detection of pancreatic neoplasia to be 75%.[7] Computed tomography is a useful aid in surgical planning.[3] Usually, insulinomas will be hyperattenuating after medium contrast injection.[19] A study showed that CT identified 10/14 primary insulinomas in dogs.[13] The bloodwork, radiographs, and ultrasound left insulinoma at the top of the differential diagnosis list. The high insulin to glucose ratio further supported the diagnoses which was later confirmed via biopsy. Treatment options for insulinomas include surgery, medical management, or a combination of both. Multiple studies report higher median survival times with surgery than medical management alone.[1,3,9] There has been controversy as far as the role of surgery for stage 2 and stage 3 patients however, studies have shown that lengthy euglycemia can be achieved in some cases.[1,12] Commonly, patients receive some medical management prior to surgery.[3]

In our patient, it was recommended to feed frequent high protein low carbohydrate meals until a partial pancreatomy was performed to remove the mass. Pancreatitis is the most common post operative complication for any pancreatic surgery, including insulinomas.[9] There are

different techniques from the suture fracture technique, blunt dissection, and use of ligasure for removal.[9] The ligasure is a bipolar sealing device commonly used to dissect tissue while maintaining hemostasis. Although the pancreas is extremely sensitive, a study showed that the use of ligasure provided shorter surgical and hospital time compared to the suture fracture technique. This study also had no incidence of post – operative pancreatitis.[21] The patients did not experience pancreatitis, but he was hyperglycemic post operatively. It is common for patients to still be hypoglycemic post-operatively but hyperglycemia post-operatively can also persist in some patients. Persistent hypoglycemia post- operatively has been shown to be a negative prognostic indicator.[1] The hyperglycemic state is hypothesized to be from suppression of the normal β -cells by tumor insulin prior to surgical removal, resulting in loss of insulin production. These patients need to be maintained on insulin therapy.[9,14] In our case, the patient's hyperglycemia resolved. For patients who do not undergo surgical therapy, medical management is another option. This can include diet changes, glucocorticoid therapy, dextrose boluses, or glucagon therapy depending on severity. Along with the other therapies listed more options for medical management include, diazoxide, octreotide, as well as streptozotocin or toceranib phosphate when metastatic disease is present.[3,4,9,18] While many studies have shown that surgery provides longer MST, some cases require medical management postoperatively as well. [14]

Definitive diagnosis can be confirmed with histopathology.[3] Insulinomas can show neoplastic cells with polygonal pleomorphic, ansiokaryotic round to oval nuclei with small single nucleolus.[10] Further confirmation can be provided using insulin immunohistochemistry staining, most insulinomas will be positive.[10] The patient's histopathology showed similar findings confirming the diagnosis of insulinoma.

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