Canine Insulinoma: A Case Report and Review of the Current Literature

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Insulinoma is a rare disease of dogs, yet it is recognized as the most common islet cell tumor of the endocrine pancreas.[1] Dogs with insulinomas often have similar clinical signs and clinical pathology data, making a presumptive diagnosis easier for a veterinarian. Arriving at a definitive diagnosis, however, requires both surgery and histopathology.[2] Veterinarians, therefore, must be aware of the biologic behavior of the tumor, the typical clinical signs and clinical pathology data, treatment options and prognostic factors in order to warrant the search for a definitive diagnosis.

An insulinoma is a functional adenocarcinoma of the beta cells of the endocrine pancreas.[3] Although most of the clinical signs are due to hyperinsulinism, insulinomas also produce serotonin, gastrin, somatostatin, and corticotropin.[4] Hyperinsulinism interrupts glucose homeostasis, causing neurologic signs associated with hypoglycemia. Neuroglucopenic signs include seizures, ataxia, weakness, muscle atrophy, apparent blindness, appendicular hyporeflexia, behavior changes and even coma.

Although they have occurred in young dogs, insulinoma occurs most frequently in middle aged to old dogs with an average age of nine years .[8] The breeds most commonly affected are German Shepherds, Irish Setters, Boxers, Golden Retrievers, and the Terrier breeds.[8,9] The prevalence of insulinomas in large breeds was also confirmed in one study where greater than 72 percent of the dogs weighed greater than 25 kilograms.[9] There is no sex predilection.[1,8,9] Unlike human insulinomas, which are often benign, greater than 75 percent of functional tumors in dogs are malignant.[8] These adenocarcinomas most commonly metastasize to regional lymph nodes and the liver in approximately 50 percent of the cases.[10]

The following case report illustrates the diagnostic approach for canine insulinoma. Furthermore, it explains one treatment option and the complications with the procedure. The discussion following compares and contrasts other findings with those of this case.

Case Report

A twelve year old spayed female mixed breed dog was referred to Iowa State University Veterinary Teaching Hospital for clinical evaluation of lethargy, behavior changes, muscle tremors, incontinence, polyuria, and polydipsia. These clinical signs had been occurring over the last month and a half. The referring veterinarian had been treating the dog with 0.01 mg/kg of thyroxine twice a day for hypothyroidism. Estrogen tablets were given twice a week for treatment of urinary incontinence. Blood chemistry revealed hypoglycemia [50 mg/dL; ref: 65-115mg/dL] and the referring veterinarian advised the owner to feed the dog four times a day. The owner was feeding a variety of commercial dog food.

On presentation to ISU Veterinary Teaching Hospital, the dog had a temperature of 101.5°F, a pulse rate of 140 beats per minute, and a panting respiratory rate. Her mucous membranes were pink, capillary refill time was less than 2 seconds, and hydration was normal. The dog weighed 7 kilograms at presentation.

A CBC was performed after physical examination. The only clinical abnormality was a slight lymphopenia. Blood chemistries were also performed and hypercalcemia [11.7 mg/dL; ref: 9.3-1 1.5 mg/dL], renal azotemia [BUN= 61 mg/dL; ref: 10-25 mg/dL] [Creatinine=2.0 mg/dL; ref: 0.5-1.5 mg/dL], hypoglycemia [50 mg/dL; ref: 65-115 mg/dL], and hyperproteinemia [7.2 g/dL; ref: 5.1-7.0 g/dL] were found. A urinalysis revealed a low specific gravity of 1.014. The

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TABLE 1: Day 1 Laboratory Results

Insulin = 26.7 μU/mL (Normal = 1-20 μU/mL)
Glucose = 50 mg/dL (Normal = 65-115 mg/dL)
IGR= 53.4 (Normal < 13.5)
AIGR= 133.5 (Normal < 30)

$$IGR = \frac{[\text{insulin}]\ \mu U/ml \times 100}{[\text{glucose}]\ mg/dL}$$

$$AIGR = \frac{[\text{insulin}]\ \mu U/ml \times 100}{[\text{glucose}]\ mg/dL - 30}$$

insulin level on this same day was found to be high [26.7 μU/ml; ref: 1-20 μU/mL]. The insulin to glucose ratio and amended insulin to glucose ratio were abnormally elevated as well (Table 1).

Abdominal radiographs were taken. Borderline bilateral decreased kidney size was identified. Ultrasound was performed to evaluate the cranial abdomen and the pancreas in particular. Using a 7.5 MHz transducer, 2D real-time ultrasonic evaluation of the abdomen revealed an 8 mm x 13 mm hyperechoic elliptical lesion in the area of the right lobe of the pancreas. No other masses were evident in the abdomen.

The patient returned approximately one week later for further evaluation and an exploratory celiotomy. Preoperatively the dog had a packed cell volume of 41.4 % and a total protein of 6.9 g/dL. The CBC was normal except for a slight lymphopenia. Blood chemistries revealed azotemia [BUN 52 mg/dL; ref: 10-25 mg/dL] [Creatinine= 2.0 mg/dL; ref: 0.5-1.5] and hypoglycemia [56 mg/dL; ref: 65-115].

Thoracic radiographs were taken and evaluated for evidence of pulmonary metastasic disease. No radiographic evidence of metastatic disease was identified.

The dog was placed in the intensive care unit the day before surgery. Lactated ringers solution with 5% dextrose and 20 mEq of potassium chloride per liter was given intravenously at a rate of 20 ml/hour.

Pre-anesthesia medications of 0.1 mg/kg of oxymorphone and 0.005 mg/kg of glycopyrrolate were given intravenously. Anesthesia was induced with thiopental at 8 mg/kg and lidocaine at 8 mg/kg intravenously. A pediatric circle using isoflurane and oxygen was used to maintain anesthesia. Lactated ringers solution with 5% dextrose was given intravenously at a rate of 5 ml/kg/hour throughout the surgery. Perioperative Cefazolin at 22 mg/kg was also given intravenously. During the surgery, intermittent positive pressure ventilation (IPPV) was employed at a breathing rate of 15 breaths per minute at a tidal volume of 105 ml. Glucose measurements were taken at the start and one hour into the surgery and were 263 mg/dL and 155 mg/dL, respectively. Blood gas analysis was performed approximately ninety minutes into the surgery. The results are listed in Table 2. Thirty minutes before surgery was complete, 0.01 mg/kg of buprenorphine was given intravenously.

A standard approach for an exploratory celiotomy was performed. Examination of the right lobe of the pancreas revealed an adhesion between the cecum and the right lobe of the pancreas. The cecal adhesions were broken down with blunt dissection and about one-third of the distal right pancreatic lobe was resected using 3-0 nylon ligatures [Ethicon]. Further examination of the abdomen revealed a discolored gastropancreatic lymph node. The entire node was removed. All tissues were submitted for histopathologic evaluation. Prior to closure the pancreas was gently palpated for any irregularities. A small pea-sized nodule was discovered in the mid-portion of the left pancreatic lobe. This nodule was removed

TABLE 2: Intraoperative Blood Gas Results

Arterial	*Sample 1*	*Sample 2*
pH	7.302	7.202
pCO_2 (mmHg)	47.3	47.0
pO_2 (mmHg)	521	462.9
HCO_3 (mmol/L)	23.5	17.8
TCO_2 (mmol/L)	25	19.3
SBE (mmol/L)	-3.1	-8.9
SAT%	100	99.8
O_2 CT Vol%	21.4	13.1
Hb (g/dL)	---	8.4
Run time	11:36	
Comments	IPPV:ISO+ 100% O_2	

by placing ligatures approximately 2 cm from both sides of the nodule and transecting the pancreas at these two points. This nodular growth was also submitted for histopathology. A small punch biopsy of the liver was taken for histopathologic examinatior although the liver appeared normal grossly. Approximately 30%-40% of the pancreas was removed in the partial pancreatectomy of the left and right lobes. No other gross abnormalities were identified on abdominal exploration.

Postoperatively, the dog was placed in the intensive care unit. The patient was placed on lactated ringers solution plus 20 mEq of potassium chloride per liter at a rate of 36 ml/hour. Buprenorphine at 0.01 mg/kg was given intravenously every six hours for two doses. Oral feedings were withheld for 48 hours postoperatively and the dog was monitored for signs of pancreatitis [eg. vomiting, abdominal pain, and increased body temperature]. Blood glucose levels were checked periodically, and a marked hyperglycemia became evident four days after the surgery. The dog was maintained on lactated ringers solution plus 20 mEq of potassium chloride per liter at a rate of 30 ml/hour on day 2 and 15 ml/hour on day 3. The dog recovered well from surgery as no fever, vomiting, diarrhea, seizures, or tremors were noted. The packed cell volume, pulse, and respiratory rate were also normal in the recovery period. Approximately 48 hours after surgery, the dog was hand fed frequent meals of bottled baby food. Approximately four days after the surgery the dog was fed Hill's I/d.© The patient was discharged five days after surgery. The owners were instructed to monitor the patient for signs of hyperglycemia [i.e. polyuria, polydipsia, and polyphagia].

Histopathology of the mesenteric lymph node revealed the replacement of approximately 95% of the normal nodal architecture by nests of neoplastic epithelial cells arranged in packets along a fine fibrovascular stroma. The cells were large with clear to eosinophilic cytoplasm and vesicular nuclei. Immunohistochemical stains of the node showed the neoplastic cells stained diffusely for insulin. A diagnosis of metastatic insulinoma was made.

The liver was within normal histologic limits. The pancreas showed areas of hemorrhage and congestion with exocrine pancreatic hyperplasia. A mild periductal lymphocytic infiltrate was also evidenced, but no neoplastic cells were witnessed. Additional sections of the pancreatic biopsy were made and evaluated. The subsequent attempt isolated neoplastic cells similar to those found in the lymph node and the diagnosis of insulinoma was confirmed in the pancreas.

Five days after discharging the dog and ten days after the surgery, the patient developed vomiting and became listless. The referring veterinarian performed blood chemistry analysis which showed azotemia [BUN= 68 mg/dL, Creatinine= 3.2mg/dL], profound hyperglycemia [686 mg/dL], increased liver enzymes [Alkaline phosphatase= 452 IU], hyperphosphatemia [phosphorus = 10.5], hyponatremia [120 mmol/L], hypochloremia [96.4 mmol/L], and hyperkalemia [5.8 mmol/L].

A urinalysis revealed a specific gravity of 1.025 and a 2+ glucose. A CBC revealed a leukocytosis and granulocytosis as well as an anemia and thrombocytosis. The referring veterinarian treated the dog with 7.5 units of NPH insulin subcutaneously. Vomiting was controlled by treating with metoclopramide at 2 mg/kg intravenously.

The dog returned to ISU the following day after seeing the referring veterinarian. Hyperlipasemia [1090U/L; ref: 0-400 U/L] was found on blood work. A diagnosis of pancreatitis was made and the dog was admitted for supportive therapy. Oral feedings were withheld for 72 hours and the patient was maintained on lactated ringers solution with 20 mEq of KCl per liter and 2 mg/kg of metoclopramide added. The fluids were given at a rate of 20 ml/hour. Three days later the patient was offered Hill's I/d© without incident. The lipase was rechecked and was decreasing. The dog was discharged five days after admittance.

Discussion

Insulin is a hormone which is part of a complex system which maintains glucose homeostasis. Insulin acts to increase stored energy by promoting glyocogenesis and inhibiting glycogenolysis by liver and muscle.[11]

In adipose tissue, insulin prevents the breakdown of fat and stimulates glycogen and fat synthesis.[12] In addition to increasing energy storage, insulin is responsible for stimulating glucose transport in certain organs such as muscle and adipose tissue.[11] The brain, however, is insulin-independent and relies on simple diffusion of glucose through the blood-brain barrier.[12] Because glucose is the major fuel for the brain and carbohydrate reserves are limited, the brain is especially sensitive to hypoglycemia.[12]

The secretion of insulin from beta cells is influenced primarily by the blood glucose concentration in the normal dog.[12] As blood glucose rises insulin is secreted and as it falls secretion is inhibited. Insulinomas, however, are often partially or fully autonomous and the normal inhibition of insulin secretion with low blood glucose is interrupted.[4] The continued insulin secretion further exacerbates the falling glucose levels by inhibiting gluconeogenesis and glycogenolysis.[12] As a result, the blood glucose level plummets until the body compensates. The hypothalamus responds to the hypoglycemia by sending stimuli to the sympathetic nervous system.[1] Epinephrine is released from the chromaffin cells of the adrenal medulla and acts directly on the liver to increase glycogenolysis.[12] Epinephrine also increases blood glucose by stimulating the release of glucagon from the alpha cells of the pancreas.[11] Glucagon acts in opposition to insulin by stimulating gluconeogenesis and glycogenolysis, thereby increasing blood glucose levels.[11] These homeostatic mechanisms, however, are unable to compete with the increased insulin levels and hypoglycemia ensues.[12] An understanding of the complex hormonal interactions in glucose homeostasis is important in elucidating the clinical signs, clinical pathology data, and management of canine insulinoma.

The dog in this case presented with intermittent signs characteristic of insulinomas. The behavior changes and lethargy were due to the neuroglycopenic effects of low glucose on the brain.[4] The muscle tremors and shaking were more related to the increased sympathetic tone in the nervous system.[4] Other evidence of increased sympathetic tone such as mydriasis, tachycardia, and hunger were not present in this case.[1,6,13] Other clinical signs of insulinomas not present in this case are blindness, head tilt, diarrhea, syncope, and exercise intolerance.[1,6,8,12] The dog did have polyuria and polydipsia which are also findings in insulinomas.[1,5]

A presumptive diagnosis of insulinoma can be made by demonstrating hyperinsulinemia with concurrent hypoglycemia and associated clinical signs.[14] Hypoglycemia alone does not indicate an insulinoma, however, as other conditions such as adrenocortical insufficiency, endotoxemia, hypopituitarism, starvation, pregnancy, exercise, and exogenous insulin administration can cause hypoglycemia.[6,12] But unlike insulinomas, these causes rarely result in a blood glucose reading of less than 40 mg/dL.[6] Whipple's triad, which consists of subnormal blood glucose concentration, clinical signs of hypoglycemia, and resolution of signs following glucose administration, is also used to tentatively diagnose insulinomas.[4,12,15]

The use of insulin to glucose ratios (IGR) and the amended insulin to glucose ratio (AIGR) in diagnosing insulinomas has been subject to considerable controversy. One study found that an insulin to glucose ration of 13.5 was necessary to increase the specificity of the ratio in diagnosing an insulinoma. This ratio, however, lacked sensitivity in many dogs. The solution was employing a fasting test in which four blood assays for glucose and insulin are done over a period of one day. The procedure was found to be safe and successful in increasing the IGR ratio sensitivity.[16] Other authors have found the use of an intravenous glucose tolerance test to be useful in diagnosis.[17] The use of this test in clinical cases, however, is limited due to the time involved in performing the test.[17] The amended insulin to glucose ratio (AIGR) is another diagnostic tool. This ratio, however, has been scrutinized for being mathematically equivalent to the IGR as well as being too sensitive.[2] The dog in this case had an IGR value of 53.4 and an AIGR value of 133.5. These values are considerably greater than the cutoff values of 13.5 and 30, respectively.[6,16] The presumptive diagnosis of insulinoma in this case was supported by using both the IGR and the AIGR.

Abdominal radiographs and ultrasound are also indicated in suspected cases of insulinoma. Abdominal radiographs may aid in detecting pancreatic neoplasia and hepatomegaly from metastasis, however, most insulinomas are not detectable on radiographs.[18] Ultrasound, on the other hand, allows better visualization of the pancreas. Insulinomas often appear as round or lobular hypoechoic masses.[18] In this case, only a hyperechoic area in the right lobe of the pancreas was detected. This region was not neoplastic but was an effect created by a cecal adhesion to the pancreas. Ultrasound can be especially helpful in localizing a neoplastic area.[18] Ultrasound is of considerable value during surgery since insulinomas can be small and may only be detected through palpation.

Another procedure which shows potential for clinical use involves staining insulinoma cells with new methylene blue prior to surgery. One study found this stain to be preferentially picked up by insulinoma cells in the pancreas as well as in metastatic sites such as lymph nodes and the liver.[19] The precise localization of tumor cells using this technique makes it an appealing adjunct in surgical treatment. The stain, however, does have adverse effects as it can cause pseudocyanosis and hemolytic anemia.[20]

In this case, partial pancreatectomy was performed under general anesthesia. Induction was accomplished with thiopental and anesthesia was maintained with isoflurane. Thiobarbiturates and inhalation agents are the preferred anesthetic agents due to their effect of decreasing cerebral glucose metabolism.[21] Intravenous dextrose was administered to prevent hypoglycemia.

Partial pancreatectomy was performed on the left lobe of the pancreas and a pea-sized tumor was removed. The method of partial pancreatectomy employed was the suture fracture technique in which the pancreas is ligated and then excised.[4,22] Another potential method is the dissection and ligation technique in which ductules and blood vessels are isolated and ligated prior to excision.[4,22] Both procedures have been demonstrated to be equally effective in preventing clinical signs due to pancreatitis in the postoperative period.[22] Approximately 30%-40% of the pancreas was removed during surgery. Although this seems abundant, up to 80%-90% of the pancreas can be removed without inducing defective fat and carbohydrate metabolism.[23] Iatrogenic exocrine pancreatic insufficiency was not a concern in this case.

Medical management is an alternative to surgical removal of insulinomas. Frequent feedings of small, high protein, low carbohydrate meals and reducing exercise may help to prevent hypoglycemia.[1,4,9,13] Drug therapy can also be instituted. Diazoxide is a benzothiadiazine with anti-insulin effects.[9,13] Diazoxide inhibits insulin secretion by blocking calcium entry into beta cells and raises blood glucose by stimulating glycogenolysis and gluconeogenesis.[1,4,12,13] The side effects, however, are numerous and include hyperglycemia, diabetes mellitus, bone marrow suppression, and gastrointestinal disturbances.[1,13] Prednisone can also be used for its gluconeogenic effects on the liver to combat hypoglycemia.[4,12,13] It also acts to decrease the sensitivity of insulin receptors.[4] A somatostatin analogue, Octreotide, has been used with equivocal results. Octreotide decreases insulin secretion after a meal in healthy dogs but has variable effects in dogs with insulinoma.[24] The ineffectiveness of the drug in only some animals is believed to be due to the lack of somatostatin analogue receptors on the tumor cells.[1,24] Other drugs with potential use are chemotherapeutic drugs such as Streptozotocin and Alloxan, which are cytotoxic to beta cells.[4,12,13] The nephrotoxicity of these drugs is severe and potentially irreversible which confines their use to only severe refractory cases.[4,12,13] Doxorubricin and other chemotherapeutics are being evaluated in human cases and have shown variable results.[4,12] Athough partial pancreatectomy is the treatment of choice, medical management of insulinomas can be used when surgery is not an option, if surgery fails to remove all the neoplastic cells, or if the tumor recurs.

The definitive diagnosis of insulinoma in this case was accomplished by histopathology of the pancreas and mesenteric lymph node. Most insulinomas occur in either the right or left lobe of the pancreas although they can occur in the body.[1,15] Fur-

Table 3: Canine Insulinoma Staging[13]

Stage I - Tumor cells only in the pancreas
Stage II - Tumor cells in the pancreas and regional lymph nodes
Stage III - Tumor cells in distant metastatic sites

thermore, most insulinomas are solitary tumors.[1] Insulinomas are staged according to their location and the presence of metastasis (Table 3).[13] This dog had stage II insulinoma as the tumor cells were present in the pancreas and the regional lymph nodes. Metastasis to distant organs as occurs in stage III insulinoma was not evidenced in this case.[13]

The prognosis of the dog in this case is guarded as metastasis to regional lymph nodes was present. Stage II insulinomas have a similar survival time as stage I but longer than stage III where distant metastasis is present.[1,10,13] Young dogs have a shorter survival time than old dogs.[1,10,13,25] The dog in this case carried a better prognosis than if it were a younger dog or if distant metastasis had occurred. The malignant nature of the tumor, however, is such that regrowth is virtually inevitable with an average survival time of 10-14 months.[1,10,14,15,25]

The dog in this case recovered well from surgery. One complication of the surgery is hypoglycemia due to incomplete tumor removal.[4,12] In this case, the dog's glucose level returned toward normal in the recovery period indicating that the tumor was successfully removed. Four days after surgery, however, the dog became hyperglycemic and symptomatic. This complication was anticipated as diabetes mellitus is known to occur after insulinoma removal.[12,23] The resulting diabetes is believed to be caused by atrophy of the normal beta cells secondary to feedback inhibition by the high insulin levels produced by the tumor.[12] The diabetic state may persist for days to months or it may be permanent.[12] The dog in this case was treated with isophane insulin (NPH insulin) and the blood glucose levels were brought to within normal limits. No additional insulin administration was necessary to maintain glucose homeostasis. This return to a normoglycemic state is a common finding as most dogs become normoglycemic in 3-5 days.[15,25]

Pancreatitis, one of the most common post-operative complications, was not observed in the immediate postoperative period.[4,12,15,21,23,25] This is likely due to good surgical technique as well as withholding food for 48 hours to quell pancreatic secretions. The patient did develop a delayed pancreatitis ten days after the surgery. The origin of this pancreatitis is questionable since pancreatitis secondary to surgery usually occurs in the first few days after surgery.[4,15,21,24] There is a possibility of the patient having subclinical pancreatitis which worsened with the surgery. The patient did recover from this bout of pancreatitis after appropriate treatment.

Conclusion

Recognizing the clinical findings of canine insulinoma is necessary in order to implement therapy in the affected dog. Other diseases can mimic the clinical signs of canine insulinoma, and thus, a thorough understanding of the disease is required in order to correctly diagnose the disease. It is a differential diagnosis one must consider when presented with clinical signs of hypoglycemia.◆

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