Diagnosis and treatment of an insulinoma in a guinea pig (Cavia porcellus)

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Case Description—A 5-year-old male guinea pig (Cavia porcellus; 0.79 kg [1.7 lb]) was examined because of a several-week history of lethargy, notable weight loss, and recurrent episodes of lateral recumbency and paddling, as though attempting to stand. Two weeks prior, the guinea pig was examined by a referring veterinarian because of lethargy and was treated with an unknown dosage of sulfadimethoxazole. Three days after the initial appointment with the referring veterinarian, the guinea pig was found flailing in lateral recumbency. The animal was brought to an emergency clinic, where blood test results showed increased liver enzyme activities of both alanine transaminase (53 U/L; reference range, 1–54 U/L) and aspartate transaminase (256 U/L; reference range, 0–90 U/L). Chemistry panel results documented hypoglycemia (45 mg/dL; reference range, 89 to 287 mg/dL) and normal blood count results were within reference limits, whereas serologic abnormalities were noted. This was confirmed upon review by a board-certified radiologist. Complete blood count results were within reference limits, whereas serum biochemical analysis showed hypoglycemia (45 mg/dL; reference range, 89 to 287 mg/dL) and normal activities of both alanine transaminase (53 U/L; refer-
During the initial visit, although the guinea pig ate well throughout the examination, it still appeared lethargic with depressed mentation. When it was found to be hypoglycemic, blood was drawn to measure insulin concentration, and the guinea pig was administered 50% dextrose solution (1 mL, PO, once) and syringe fed a hand feeding formula meant for herbivores; after which the guinea pig appeared stronger. The owner was instructed to continue syringe feeding the formula at home (15 mL, PO, q 8 h if not eating), instead of giving corn syrup orally, to try to prevent potential dramatic surges and declines in blood glucose and insulin concentrations. The patient was also prescribed a probiotic supplement (1 g, PO, q 24 h for 14 days) for potential dysbiosis.

Measurement of insulin concentration analyzed at a commercial laboratory showed notable hyperinsulinemia (>1,440 pmol/mL [< 201 μU/L]; no reported values for guinea pigs), with concurrent hypoglycemia (0.6 mmol/L [11 mg/dL]) and an elevated insulin-to-glucose ratio (>2,400 pmol/mmol; no reported values for guinea pigs). Given the considerably elevated insulin concentration in the face of hypoglycemia, a presumptive diagnosis of insulinoma was made.

Approximately 1 week following the initial visit, the guinea pig was reexamined, and an abdominal ultrasonographic examination was performed. The owner reported that the guinea pig was eating well at home but episodically appeared weak, at which point she syringe fed formula as previously instructed, and the animal would improve. Abdominal ultrasonographic examination revealed mild hepaticomegaly with no parenchymal changes, a scant amount of peritoneal effusion, a normal-sized pancreas, and no obvious hepatic or pancreatic nodules.

Because of the animal’s persistent episodes of weakness and hyperinsulinemia concurrent with hypoglycemia, the guinea pig was prescribed diazoxide at 4 mg (5 mg/kg [2.3 mg/lb], PO, q 12 h). After 7 days of treatment, the guinea pig was returned to the hospital for blood glucose curve measurement. An intravenous catheter was placed in the lateral saphenous vein to facilitate repeated blood collection; however, the catheter clotted after the first 3 samplings. Thus, serial venipuncture with a 100 U/mL syringe and 33-gauge needle was used to obtain the remaining measurements. The samples were run on a point-of-care glucometer with samples of whole blood. As the first blood glucose measurement indicated severe hypoglycemia (33 mg/dL), the next diazoxide dosage was doubled from the previously administered 5 mg/kg to 10 mg/kg (4.5 mg/lb), PO, every 12 hours. After a subsequent blood glucose measurement 12 hours later that showed persistent hypoglycemia (42 mg/dL), the next diazoxide dosage was increased again to 15 mg/kg (6.8 mg/lb), PO, every 12 hours. Despite this increase, the guinea pig remained hypoglycemic (46 mg/dL) 7 hours later. Consequently, the dosage of diazoxide was increased to 25 mg/kg (11.4 mg/lb), PO, every 12 hours.

Approximately 1 week after increasing the dosage, the owner reported that the guinea pig was doing well. A second blood glucose curve was measured approximately 12 days following the initial curve. This second curve demonstrated that the guinea pig’s blood glucose remained within the reference range (reference range, 89 to 287 mg/dL) throughout the 12-hour study. The initial blood glucose concentration measured in the morning was 85 mg/dL. The morning dose of diazoxide at 25 mg/kg was administered 3 hours later, at which point the blood glucose concentration was 91 mg/dL. Nine hours after the initial measurement, the blood glucose concentration was 132 mg/dL.

The guinea pig thrived for approximately 3 weeks on the higher (25 mg/kg, PO, q 12 h) diazoxide dosage. The animal was then reexamined at the hospital because of abdominal distension and potential constipation. On physical examination, the guinea pig had a moderately distended abdomen and signs of mild discomfort on palpation. There was no stool present in the anus, nor was there evidence of fecal staining in the perineal region. Abdominal radiography revealed notable gas distension of the stomach extending caudally to the sacrum. A board-certified radiologist’s review of these radiographs reported considerable gastrointestinal distension with gas, which was interpreted to be more consistent with gastrointestinal stasis, instead of an obstruction. An abdominal ultrasonographic examination was recommended if distension did not resolve with supportive care. The animal was administered 50 mL of lactated Ringer’s solution, SC, and the owner was sent home with instructions to give a lubricant stool softener (1 mL, PO, q 12 h).

The following morning, the guinea pig was found dead by the owners at home. The guinea pig had not passed stool overnight, and its abdomen remained distended. Necropsy showed a moderate amount of serous abdominal effusion. The liver was diffusely tan, firm, and mildly thickened. The stomach, cecum, and sacculated region of colon all were distended with gas, and the colon and cecum both contained a large amount of watery stool. Intestinal loops were adhered to each other and to the pancreas, just caudal to the liver in the region of the caudal vena cava. A large, approximately 1 × 1-cm purple mass was present in the pancreas adjacent to the adhesions. The lungs contained large multifocal irregular pale yellow regions. There was a small amount of serous pericardial effusion.

Representative tissue samples of coelomic organs were collected and placed in neutral-buffered 10% formalin solution prior to being processed routinely. Paraffin-embedded tissues were sectioned at approximately 5 μm, mounted on glass slides, and stained with H&E. These included pancreas, spleen, kidney, liver, intestines, stomach, heart, trachea, thyroid gland, esophagus, lung, cerebrum, and cerebellum. Histologic evaluation identified a pancreatic islet cell tumor characterized as an encapsulated expansile mass composed of cords and nests of polygonal cells with abundant cytoplasmic vacuolization and variably distinct cytoplasmic borders (Figure 1). The pale basophilic cytoplasm was expanded with multiple coalescing clear vacuoles. The cell nuclei were oval with a vesicular chromatin pattern and 1 to 2 indistinct basophilic nucleoli (Figure 2). The mitotic index was rare at <1/10 hpf. These cells were...
supported on a severely congested fine fibrovascular connective tissue. The tumor compressed adjacent lobules of pancreatic acinar cells. The liver was supporting diffuse cytoplasmic vacuolization of coalescing clear vacuoles. No lesions were noted affecting the other tissues. The findings were consistent with an islet cell tumor (insulinoma) and vacuolar hepatopathy, the latter of which was deemed consistent with abnormalities of glucose metabolism.

Discussion

To our knowledge, insulinoma (functional beta-cell tumor predominantly producing insulin) has never before been diagnosed before death in a guinea pig and thus has never been treated. Before death, a presumptive diagnosis was made when the guinea pig was determined to have hypoglycemia concurrent with hyperinsulinemia. After death, the diagnosis was confirmed via histologic analysis.

When the guinea pig of this report was first examined at our hospital, clinical abnormalities aside from those directly related to hypoglycemia included hepatomegaly reported on a previous ultrasound examination, a mild head tilt with chronic otitis media confirmed via radiography, and abdominal distension. Hepatic disease was not thought to be the cause of the hypoglycemia, as the rest of the blood work was within reference limits including liver enzyme activities. As there are no published guinea pig CBC or chemistry reference intervals for the point-of-care analyzer used, both a well-established rodent text and a formulary focusing on exotic animals were consulted instead. In addition, whereas hepatic disease could not be truly discounted without a tissue sample, repeated abdominal ultrasonography demonstrated only mild hepatomegaly without any parenchymal changes. Similarly, additional diagnostic tests and treatment were not pursued regarding the otitis media. This was deemed to be a chronic condition because of the degree of bony proliferation noted on radiographic analysis of the bullae, and as the animal was only mildly clinical (slight head tilt), diagnostic and treatment efforts were focused on the hypoglycemia. Lastly, the abdominal distension was hypothesized to be secondary to possible ileus and secondary dysbiosis, which may develop in inappetent guinea pigs.

As noted, there are no reported reference values for insulin or insulin-to-glucose ratios in guinea pigs. Insulinomas are widespread tumors in ferrets, relatively common in dogs, and infrequent in cats. For ferrets, a reference interval has been reported ranging from 4.88 to 34.84 µU/mL, and for dogs, a reference interval has been established ranging from 5 to 20 µU/mL. The value reported in this guinea pig was comparatively notably elevated, at > 201 µU/L, which, concurrent with a glucose concentration of 11 mg/dL, supported a diagnosis of insulinoma.

When the guinea pig was reexamined after 3 weeks of diazoxide treatment with severe gastrointestinal gas distention, dysbiosis, gastrointestinal obstruction, and...
torsion were all considered as differential diagnoses. Severe dysbiosis secondary to ileus was thought to be most likely given that the animal did not have access to ingesta and the gas pattern was interpreted as consistent with dysbiosis. The owners did not wish to pursue further diagnostic tests at this point, and supportive care was elected. Pain medication was not provided, as it would be difficult for the owners to monitor for a hypoglycemic episode if the animal was sedated. Fluid therapy was provided, as ileus often leads to a loss of fluid from ingesta, leading to dehydration of intestinal contents, which often exacerbate the ileus. A stool softener was provided in case the animal was truly constipated. Unfortunately, on necropsy, neither the abdominal fluid nor the bullae were analyzed.

Insulinomas are common in ferrets, infrequent in dogs, and even less common in cats. In ferrets, most insulinomas reportedly do not metastasize; however, they spread via local invasion predominantly to the liver, spleen, and regional lymph nodes. Clinical signs in ferrets stem mainly from hypoglycemia and include opisthotonos, dullness, hind limb weakness, and ataxia. Seizures secondary to hypoglycemia are rare. Diagnosis is typically made by documentation of hypoglycemia in the face of normal or elevated blood insulin concentration. Diagnosis is supported by ultrasonographic visualization of pancreatic nodules. Surgical resection is typically recommended in otherwise healthy ferrets, with the goal of completely resecting solitary tumors or debulking nonresectable tumors. In patients with metastasis, nonresectable tumors, elderly ferrets, or ferrets with concurrent disease, medical management is often elected.

In contrast, most insulinomas in dogs are malignant with metastasis having already occurred at the time of diagnosis. Metastasis is most common to regional lymph nodes and mesentry, and pulmonary metastasis is rare. Clinical signs in dogs include weakness, ataxia, and collapse, progressing to seizure activity. Dogs with chronic mild hypoglycemia appear to acclimate and may have prolonged periods of clinically normal activity. Physical examination is often unremarkable, with lethargy and weakness being the most common abnormalities. The only consistent clinical pathology abnormality in dogs with beta-cell tumors is hypoglycemia. Diagnosis and treatment options are similar to those in ferrets.

In both ferrets and dogs, medical treatment typically consists of long-term oral glucocorticoid (typically prednisone or prednisolone) administration, along with recommendations for multiple small meals throughout the day and avoidance of foods containing simple carbohydrates. Prednisone stimulates hepatic gluconeogenesis and glycogenolysis and antagonizes the effects of insulin, whereas diet adjustment helps decrease repeated stimulation of insulin release by keeping blood glucose concentrations more constant. If prednisone treatment becomes ineffective, or if the patient develops important adverse effects, diazoxide is often added to the treatment regimen, and the prednisone dosage is decreased. Diazoxide inhibits insulin release, stimulates hepatic glycogenolysis and gluconeogenesis, and inhibits peripheral glucose uptake. Two less frequently used medications include octreotide (a somatostatin analogue), which inhibits insulin secretion, and streptozocin, which is a chemotherapeutic agent that is selectively toxic toward pancreatic beta cells. As these medications are even less well studied in the treatment of insulinoma than diazoxide and streptozocin, they can also cause severe adverse effects, including nephrotoxicosis, pancreatitis, and vomiting, neither medication was used in the treatment of this guinea pig.

Surgery was not pursued in this guinea pig, as there was no identifiable mass on abdominal ultrasound examination, and medical treatment was initiated instead. It is difficult to adjust diet in guinea pigs, as they are herbivorous mammals that normally should eat high-fiber food constantly throughout the day. Foods containing simple carbohydrates should always be avoided in guinea pigs, as carbohydrate ingestion in guinea pigs can lead to intestinal pH changes, subsequent dysbiosis, and gastrointestinal stasis. Glucocorticoids (prednisone and prednisolone) are the first line of medical treatment in affected dogs and ferrets. Whereas, to our knowledge, there are no specific studies, there are multiple anecdotal reports of prednisone-induced immunosuppression in both guinea pigs and rabbits, potentially leading to secondary infection with *Mycoplasma* spp, *Bordetella* spp, *Pasteurella* spp, and, specifically in rabbits, *Encephalizozoan cuniculi*, especially in previously subclinical carriers. Rabbits are reported to be a glucocorticoid-sensitive species, developing secondary immunosuppression and hepatotoxicity, regardless of administration method. Prednisone has also been anecdotally reported to cause gastrointestinal ulceration and perforation in rabbits. Since both guinea pigs and rabbits are herbivores with similar gastrointestinal anatomy and physiology (monogastric hindgut fermenters), guinea pigs may also be predisposed to developing gastrointestinal ulceration and possible perforation secondary to long-term prednisone administration. In addition, guinea pigs are subclinical carriers for infectious organisms such as *Bordetella bronchiseptica*. Because of the potential for immunosuppression and gastrointestinal ulceration, the guinea pig of this report was treated initially with diazoxide, rather than prednisone. As no published reports documenting a dosage of diazoxide to treat hypoglycemia in guinea pigs could be found, the low end of the recommended dosage for ferrets (3 mg/kg, PO, q 12 h) was chosen as a starting point. In ferrets, the dosage is typically gradually increased to 30 to 60 mg/kg (13.6 to 27.3 mg/lb), PO, every 12 hours if normoglycemia is not obtained with lower dosages. This is similar to dosing recommendations in dogs as well, where the initial dosage is typically 5 mg/kg, PO, every 12 hours up to but not > 60 mg/kg/d. For the guinea pig of the present report, the diazoxide dosage was increased to 25 mg/kg, PO, every 12 hours, at which point the second glucose curve measurements demonstrated attainment of normoglycemia.

To our knowledge, the case described in this report is the only documented case of insulinoma treatment in a guinea pig. One previous report describes diagnoses of insulinoma in 2 guinea pigs after death. Both guinea pigs were approximately 5 years old and had...
abnormal neurologic signs such as torticollis, hemiparesis, twitching, ataxia, and seizures. The first guinea pig was reported to have had hypoglycemia twice, and the owner was instructed to administer a 25% dextrose solution orally when the animal developed abnormal neurologic signs. That guinea pig was ultimately euthanized. Prior to euthanasia, blood was drawn for measurement of glucose and insulin concentrations, which were 4.6 mmol/L (84 mg/dL; reference range, 89 to 287 mg/dL) and < 3 µg/L, respectively. However, it was later discovered there had been a 4-day delay in sample delivery, making it unlikely that the serum samples had remained frozen and potentially altering glucose and insulin concentration results. At necropsy, a 3-mm red mass noted in the pancreas was confirmed by histologic analysis to be an insulinoma. The second guinea pig with reported insulinoma had abnormal neurologic signs and concurrent hypoglycemia, and following oral administration of dextrose solution, its clinical signs resolved. The guinea pig was euthanized, and necropsy revealed a 1-cm red mass in the pancreas confirmed via histiologic analysis to be an insulinoma. Both animals in that report14 had clinical signs similar to those seen in the patient of the present case report. In addition, metastases were not reported.14

Because notable histopathologic lesions aside from the pancreatic islet cell tumor and vacuolar hepatopathy were not found in our patient, it is unclear exactly why the guinea pig of this report died. On the basis of necropsy findings, it is possible that the insulinoma was large enough to interfere with gastrointestinal function or led to intestinal adhesions and subsequent partial gastrointestinal tract obstruction. It is unlikely there was complete obstruction, given the large amount of stool in the large intestine. Another possibility is that as a result of discomfort induced by the neoplasm, the guinea pig became inappetent and developed subsequent dysbiosis and gastrointestinal stasis, which, if allowed to progress, can lead to enterotoxemia, sepsis, and death.5 Another possibility is that the guinea pig developed gastrointestinal adverse effects of diazoxide. Reported adverse effects of diazoxide in ferrets and dogs include inappetence, ptysialgia, diarrhea, and vomiting.15 Although there is no published dosage for diazoxide in guinea pigs and the effects of diazoxide have not been studied in guinea pigs, it is possible the guinea pig of the present report developed gastrointestinal adverse effects similar to those reported in ferrets and as a result developed inappetence with secondary dysbiosis and gastrointestinal stasis. However, the latter seems less likely, as the guinea pig did thrive for 3 weeks on the higher diazoxide dosage and likely would have developed clinical signs of gastrointestinal stasis secondary to diazoxide earlier in the treatment course.

Although there are few reports of insulinomas in guinea pigs, this disease may be more prevalent than previously documented and may go widely unreported in cases where owners elect euthanasia or where abnormal neurologic signs are attributed to other diseases. Further research is needed to document adverse effects of prednisone administration in guinea pigs and to determine whether prednisone is a safe treatment option. In addition, more information is also needed on potential adverse effects of diazoxide treatment in herbivorous animals such as guinea pigs and rabbits, in which slight inappetence or nausea might lead to notable gastrointestinal abnormalities. As this report demonstrates, diazoxide treatment can effectively combat the signs of hypoglycemia in guinea pigs and has potential for long-term medical treatment for guinea pig insulinomas. The appropriate dosage regimen and possible long-term adverse effects of diazoxide administration in rodents must be studied. Although further studies of diazoxide treatment in guinea pig insulinomas are needed, the present case shows that diazoxide treatment, along with feeding small, frequent, complex carbohydrate–containing meals, can improve quality of life and extend the life span in guinea pigs with hypoglycemia as a result of insulinoma.

References