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<증례보고>

Hyperinsulinism in a dog with beta-cell neoplasia (insulinoma)

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Abstract : A six-year-old female cocker spaniel presented with recurring episodes of pelvic limb weakness and intermittent seizures. Laboratory analysis revealed marked hypoglycemia and an elevated serum insulin concentration. A pancreatic beta-cell tumor at stage III ($T_1N_1M_1$) was diagnosed based on serial blood glucose and insulin measurements along with diagnostic imaging. The patient survived for 140 days after diagnosis with medical management, including frequent feeding and prednisolone therapy. On necropsy, necrosis and masses in the peripancreatic omentum and liver were found; pancreatic beta-cell neoplasia with metastasis to the liver was confirmed by histopathologic examination. This case reports hyper-insulinism in a dog presenting with hypoglycemic seizures.

Keywords : hypoglycemia, insulin-glucose ratio, insulin-secreting islet cell neoplasia, insulinoma, seizure

Introduction

Functional beta-cell tumors, often called insulinomas, arise from the neoplastic transformation of beta-cells within the endocrine pancreas; these cells comprise 60% to 70% of pancreatic islet cells [10]. This neoplasm is uncommon in dogs with most cases being malignant [8]. Clinical signs attributable to insulinomas are usually caused by insulin-induced hypoglycemia. Prognosis is poor with median survival times for stage I, II, and III tumors of 785 days, 547 days, and 217 days, respectively [12]. Medical treatment involves the feeding of multiple, small meals low in simple carbohydrates with corticosteroid therapy being recommended when surgical therapy is declined, inappropriate, or unsuccessful due to the presence of multiple or inoperable primary tumors or metastatic disease [5, 10]. Here we report a case of a dog presenting with hypoglycemic seizures that were diagnosed as resulting from a canine beta-cell neoplasm.

Case report

A six-year-old female cocker spaniel presented to the Chonbuk Animal Medical Center, Jeonbuk, Korea. The pertinent clinical findings were recurring episodes of pelvic limb weakness and intermittent collapse lasting approximately 20 minutes each during the prior three weeks.

The complete blood counts, general serum biochemistry profiles, and thoracic and abdominal radiographic findings were unremarkable, except for marked fasting hypoglycemia (43 mg/dL). The differential diagnoses for hypoglycemia in dogs include hepatic disease, sepsis, hypoadrenocorticism, and beta-cell neoplasm. Hepatic disease was considered unlikely as the serum bile acids were within reference intervals. Sepsis was also ruled out based on the normal leukogram with appropriate counts. The absence of electrolyte abnormalities did not support hypoadrenocorticism; in addition the subject had a normal adrenocorticotropic hormone stimulation test.

Persistent hypoglycemia was confirmed by serial

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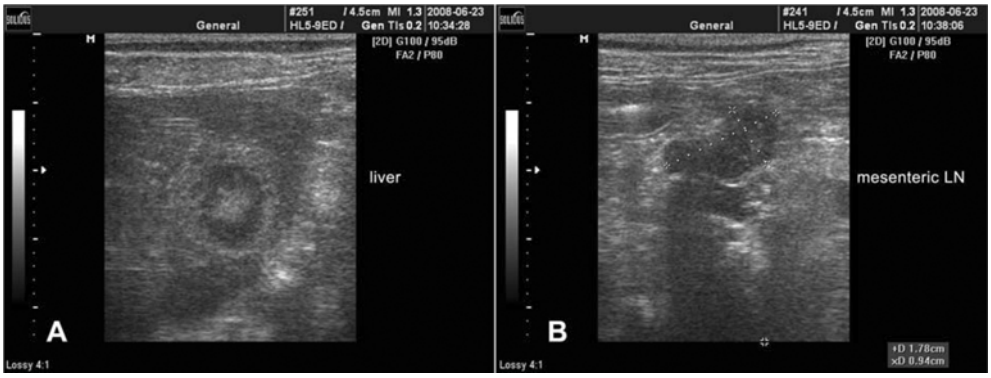

Fig. 1. Abdominal ultrasound examination in a dog with pancreatic beta-cell neoplasia (insulinoma). (A) Solid hypoechoic lesion in the liver parenchyma; (B) mesenteric lymph node enlargement.

blood glucose studies and low serum fructosamine concentrations (190 μmol/L). Simultaneously, the fasting serum insulin concentration was remarkably high (91.72 μU/mL, reference range 2.6 to 25 μU/mL); this observation greatly increased the suspicion of a beta-cell neoplasm**.** Though pancreatic tumors cannot be visualized by abdominal ultrasound examination and computed tomographic angiography, a solid mass in the liver and mesenteric lymph node enlargements were identified (Fig. 1). The tumor stage was III ($T_1N_1M_1$) according to the World Health Organization tumor-node-metastasis system.

The patient survived for 140 days with medical management including four to six meals daily and prednisolone (0.5 mg/kg, BID) therapy. An infusion of glucagon, ranging from 5 to 15 ng/kg/min, was also used in emergency management. Initially, the blood glucose level (41 to 148 mg/dL) and insulin concentration (4.76 to 11.31 μU/mL) remained stable, however, hypoglycemic crisis eventually recurred and temporary blindness was detected. At necropsy, multiple nodules and masses of varying size were observed in the peripancreatic omentum and liver. Tissue samples from the organs, including the pancreas and liver, were collected, fixed in neutral-buffered 10% phosphate-buffered formalin, and processed by standard histological paraffin methods. Tissue was sectioned at 5 μm, was stained with haematoxylin and eosin, and examined by light microscopy. As demonstrated in Figs. 2A and B, the majority of the pancreas was composed of neoplastic islet cells, indicating a beta-cell tumor. Furthermore, neoplastic beta-cells metastasized to the liver, indicating that beta-cell carcinoma had already invaded blood vessels and/or lymphatics (Fig. 2C).

Discussion

This case reports an insulinoma in a dog that presented with hypoglycemic seizures. The clinical signs of hypoglycemia are the result of both decreased glucose supply to the brain and stimulation of the counter-regulatory sympathoadrenal system [5]. When blood glucose concentrations decrease below a critical level, cerebral oxidation decreases, and neuroglycopenic signs such as lethargy, weakness, ataxia, altered mentation, seizures, and coma result [3]. Therefore, these clinical signs are episodic, and rapidly alleviated by the administration of glucose. Although the histopathologic examination of the brain tissue was not performed in this case, the repeated episodes of hypoglycemia might cause irreversible neuronal degeneration and lead to coma and death in the end [3].

The “gold standard” diagnostic evidence for insulinoma is detection of excessive insulin secretion in the presence of hypoglycemia and was observed in this case. Abdominal and thoracic radiographs are typically unremarkable due to small tumor size and the lack of radiographically detectable pulmonary metastasis in veterinary medicine [5, 6, 9, 10]. Instead, these imaging modalities may be of considerably greater benefit in suggesting the presence of lymph node involvement or hepatic metastasis. This imaging may also aid in identifying other hypoglycemia-producing diseases [5]. On the other hand, demonstration of high serum insulin concentrations in the presence of hypoglycemia is highly suggestive of an insulinoma

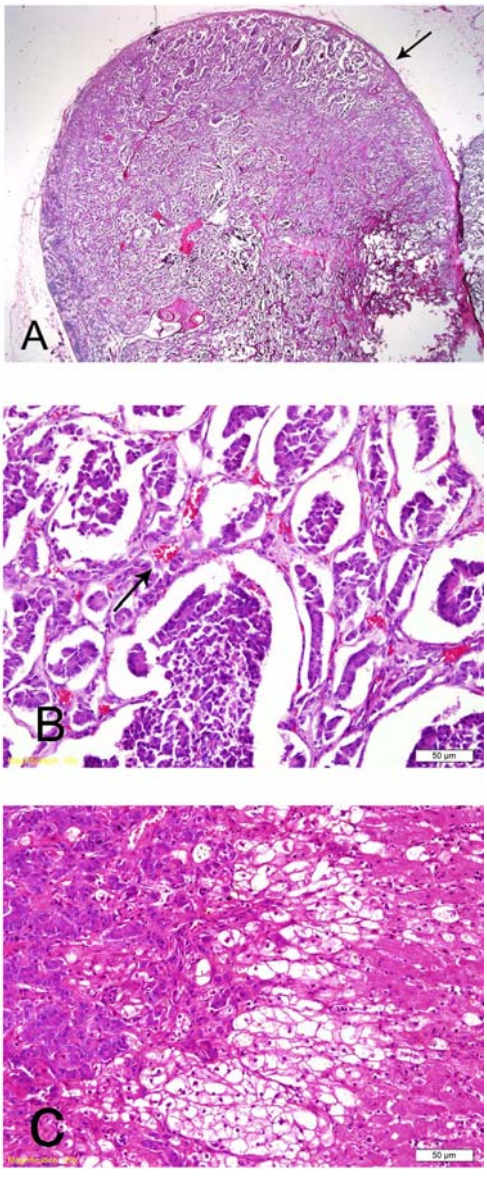

Fig. 2. Histological imaging of an insulinoma mass in the pancreas and liver of a dog with a pancreatic beta-cell tumor. (A) Beta-cell carcinoma of pancreatic islets. The neoplasm is encapsulated by a fibrous capsule (arrow) and is well demarcated from the adjacent pancreas tissue (H&E, ×12.5). (B) An arrangement of beta-cell carcinoma cells that resemble the structure of normal pancreas islets. Fine connective tissue and capillaries (arrow) are located between the neoplastic beta cells (H&E, ×400). (C) Metastatic beta-cell carcinoma of the liver. Ballooning degeneration of hepatocytes caused by corticosteroid treatment was observed at the border (central portion) between the neoplastic area (left portion) and adjacent liver tissue (right portion) (H&E, ×400).

[5]. If serum insulin levels are above the normal range at the time of hypoglycemia, or even near the upper range of normal, a diagnosis of an insulinoma is highly likely. Occasionally, sepsis and non-pancreatic neoplasms have been documented as having inappropriately elevated serum insulin levels during hypoglycemia [2]. Although the use of insulin to glucose ratio (IGR) or amended IGR (AIGR) is not advocated by some authors [1, 2, 4, 7], the values in this case were 35 U/mol and 705 μU/mg (an IGR of > 4.2 and an AIGR of > 30 are consistent with insulinoma) [13, 16]; these values are also considered diagnostic. Provocative testing, including glucagon, glucose, and tolbutamide tolerance tests; an epinephrine stimulation test; an L-leucine test; a calcium-infusion test; and oral glucose tolerance test, has been assessed as a diagnostic tool for insulinoma, but these tests have not been shown to be more sensitive than the insulin-glucose pair and can be time-consuming, expensive, and dangerous to the patient by potentiating significant hypoglycemia [15]. Further studies are needed to evaluate the sensitivity of IGR and AIGR in detecting the presence of insulinomas.

For long term treatment of this case, dietary modifications and prednisolone were used. For the emergency management of hypoglycemia, an infusion of glucagon (10 ng/kg/min) is usually used and shown to be beneficial. However, octreotide (10 μg, BID), a somatostatic analogue, *via* subcutaneous administration was not found to be beneficial for this patient. Indeed, the responsiveness of dogs to octreotide is known to be variable despite having an appropriate receptor subtype [11, 14]. The lack of a dependable response to octreotide in dogs may be due to the drug's inhibition of glucagon and growth hormone secretion. If suppression of glucagon and growth hormone secretion is of greater magnitude and duration compared with the suppression of insulin secretion, octreotide may actually worsen the hypoglycemia. Also, some canine insulinomas may not have somatostatin receptors [8]. Surgical resection was not performed in this case due to the poor prognosis. This case reports an insulinoma in a dog presenting with hypoglycemic seizures.

References

1. **Best JD, Chisholm DJ, Alford FP.** Insulinoma: poor

recognition of clinical features is the major problem in diagnosis. Med J Aust 1978, **2**, 1-5.

2. **Breitschwerdt EB, Loar AS, Hribernik TN, McGrath RK.** Hypoglycemia in four dogs with sepsis. J Am Vet Med Assoc 1981, **178**, 1072-1076.
3. **Capen CC.** Tumours of the endocrine glands. In: Meuten DJ (ed.). Tumors in Domestic Animals. 4th ed. pp. 684-688, Iowa State Press, Ames, 2002.
4. **Edwards DF.** It's time to unamend the insulin-glucose ratio. J Am Vet Med Assoc 1986, **188**, 951-953.
5. **Feldman EC, Nelson RW.** Canine and Feline Endocrinology and Reproduction. 3rd ed. pp. 616-644, Saunders, St. Louis, 2004.
6. **Fernandez NJ, Barton J, Spotswood T.** Hypoglycemia in a dog. Can Vet J 2009, **50**, 423-426.
7. **Floyd JC Jr, Fajans SS, Pek S, Chance RE.** A newly recognized pancreatic polypeptide; plasma levels in health and disease. Recent Prog Horm Res 1976, **33**, 519-570.
8. **Hess RS.** Insulin-secreting islet cell neoplasia. In: Ettinger SJ, Feldman EC (eds.). Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat. 6th ed. pp. 1560-1563, Elsevier Saunders, St. Louis, 2005.
9. **Kruth SA, Feldman EC, Kennedy PC.** Insulin-secreting islet cell tumors: establishing a diagnosis and the clinical course for 25 dogs. J Am Vet Med Assoc 1982, **181**, 54-58.
10. **Lurye JC, Behrend EN.** Endocrine tumors. Vet Clin North Am Small Anim Pract 2001, **31**, 1083-1110.
11. **Meleo K.** Management of insuloma patients with refractory hypoglycemia. Probl Vet Med 1990, **2**, 602-609.
12. **Polton GA, White RN, Brearley MJ, Eastwood JM.** Improved survival in a retrospective cohort of 28 dogs with insulinoma. J Small Anim Pract 2007, **48**, 151-156.
13. **Siliart B, Stambouli F.** Laboratory diagnosis of insulinoma in the dog: a retrospective study and a new diagnostic procedure. J Small Anim Pract 1996, **37**, 367-370.
14. **Simpson KW, Stepien RL, Elwood CM, Boswood A, Vaillant CR.** Evaluation of the long-acting somatostatin analogue octreotide in the management of insulinoma in three dogs. J Small Anim Pract 1995, **36**, 161-165.
15. **Steiner JM, Bruyette DS.** Canine insulinoma. Compend Contin Educ Pract Vet 1996, **18**, 13-23.
16. **Thompson JC, Jones BR, Hickson PC.** The amended insulin to glucose ratio and diagnosis of insulinoma in dogs. N Z Vet J 1995, **43**, 240-243.