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Scientific Report

Diagnosis and management of hypoglycaemia due to pancreatic insulin-secreting neoplasia in a German shepherd dog

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Summary

A 7-year-old castrated male German shepherd dog was presented with a 10-day history of intermittent lethargy, weakness and episodic seizures. Laboratory findings after admission revealed hypoglycaemia and hyperinsulinaemia. Provisional diagnosis of insulinoma was made based on the presence of concurrent hypoglycaemia and elevated insulin level. In exploratory laparotomy a small nodular mass was detected on the pancreas. Other abdominal organs were normal in gross inspection. The mass was removed surgically. Histopathology of the excised pancreatic nodule confirmed the diagnosis of insulinoma. The dog became seizure free following the surgical operation.

Key words: Insulin-secreting neoplasia, Hypoglycaemia, Dog

Introduction

Beta-cell tumours of the pancreas originate from specialized neuroendocrine cells that synthesize and secrete peptide hormones. Tumours that develop from these cells are named based on hormone they secrete (e.g., insulinoma), and clinical signs are attributed to the peptide that is produced (Pilny and Chen, 2004). Insulinomas have been described in humans, dogs, cats, ferrets and guinea pigs (Leifer *et al*., 1986; Elie and Zerke, 1995; Kraje, 2003; Tongson-Ignacio *et al*., 2005; Vannevel and Wilcock, 2005). However, it seemed that these tumours are uncommon in dogs and extremely rare in other domestic animals (Ogilvie, 1996). These tumours are small but have potent physiological effects (Parker *et al*., 1981). Large breed dogs, such as Irish setters, Boxers, German shepherds, and Fox terriers are predisposed to insulinoma, although it may occur in any breed (Vallee, 2003). The present report describes diagnosis and clinical management of hypoglycaemia in a German shepherd dog with insulinoma.

Case history

A 7-year-old castrated male German shepherd dog was presented with a 10-day history of intermittent episodic lethargy, weakness and episodic seizures. Physical examination revealed that the dog was restless, recumbent and had signs of depression. Ten minutes after admission, during the radiographic examination, the dog showed grand mal seizures.

Diazepam was administered (2 mg/kg) by intravenous infusion which was resulted in resolution of seizure attack. But seizure activity recurred after 30 min. Results of

serum biochemical profile revealed hypoglycaemia [a](43 mg/dl, normal range, 71-115 mg/dl). The blood glucose level was determined by photometry (Pars Azmon Company, Karaj, Iran). Following administration of intravenous dextrose (50%, 1 ml/kg), recurrent episodes of seizures was completely resolved. The exact cause of hypoglycaemia could not be determined at this time. The dog showed weakness and subsequent collapse after 3 h but seizure did not observe. To investigate the possibility of hypoglycaemia as a predisposing factor in the development of weakness and seizures, second blood sample was obtained. Laboratory findings showed hypoglycaemia (48 mg/dl). Other laboratory findings such as CBC and serum electrolyte concentrations were within normal limits (Table 1). Thoracic and abdominal radiographs, and abdominal ultrasonography were unremarkable. The dog responded well to administration of intravenous dextrose; 15 min following administration of dextrose, the dog became alert and bright and could stand. Based on the two blood samples that showed hypoglycaemia and normal results of other tests, a provisional diagnosis of insulinoma was made. The owner was instructed to feed multiple small meals to prevent sudden onset of hypoglycaemia and subsequent complications. In the following day, the blood glucose level was measured hourly until reached 37 mg/dl, at this time, blood insulin level was measured 32 µU/ml [b](normal range, 5-20 µU/ml). The insulin concentration was measured by chemiluminescent immunoassay (LIASON insulin (310360), DiaSorin S.P.A. Italy).

Concurrent occurrence of hypoglycaemia and elevated serum insulin level (insulin/glucose ratio: 0.86), increased the possibility of insulinoma as a tentative diagnosis and the dog referred for exploratory laparotomy. On surgical exploration of abdominal cavity, a small nodular mass was detected on the pancreas. Other abdominal organs were normal in gross inspection. The mass was removed surgically. Recovery from surgery was uneventful. Histological examination of the mass revealed the massive proliferation of the endocrine tissue. The tumour consisted of small solid packets of polygonal epithelial cells which defined by a delicate fibrovascular stroma and consisted of a network of small inconspicuous blood vessels (Fig. 1). The neoplastic cells were well-differentiated and had scant to moderate lightly eosinophilic cytoplasm and

Table 1: Haematological and serum biochemical analysis in the presented case during the admission

Blood parameters	Value	Reference range
White blood cells ($\times10^3$/µl)	8	6-15
Neutrophils ($\times10^3$/µl)	6	3-11.5
Lymphocytes ($\times10^3$/µl)	1.6	1-4.8
Eosinophils ($\times10^3$/µl)	0.4	<1.3
Urea (mg/dl)	9.5	8.4-19.6
Sodium (mEq/L)	147	140-153
Potassium (mEq/L)	4.2	3.8-5.3
Calcium (mg/dl)	9.7	8.8-10.8
Total protein (g/dl)	6.3	5.7-7.8
Albumin (g/dl)	2.9	2.3-3.1

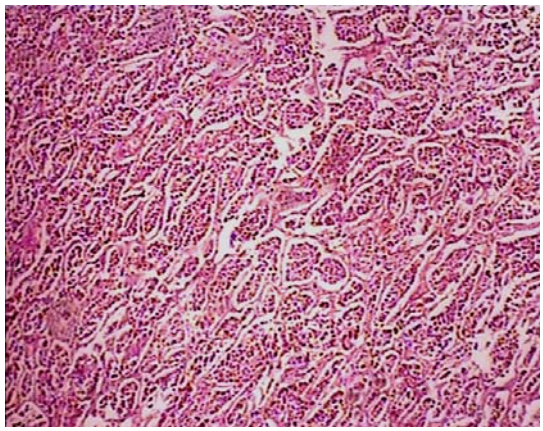

Fig. 1: The cells are arranged into acini, separated by fibrovascular septa. The exocrine tissue is not present, (H&E, ×40)

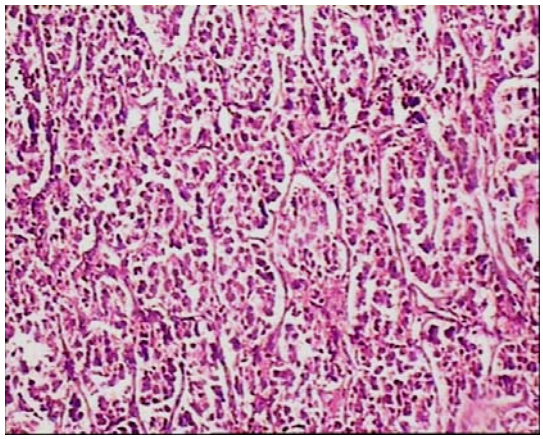

Fig. 2: The closely packed of neoplastic cells (nesting pattern) are obvious. The same figure with higher magnification, (H&E, ×100)

deep basophilic nucleous with indistinct cell borders (Fig. 2). Mitotic figures were not seen. The histologic appearance considered as insulinoma. However, the dog became seizure free during a follow-up period of 11 months.

Discussion

Hypoglycaemia was the initial serum biochemical finding in our case. Hypoglycaemia is a relatively uncommon but potentially life-threatening problem in small animals (Kenneth and Cook, 1998). The term hypoglycaemia has two level of usage in medical literature. The most general usage is to indicate that the blood glucose concentration is below the lower limit of a statistically defined range of values for healthy individuals. However, an individual could have a blood glucose concentration below the normal range without exhibiting clinical signs. For example, the normal range of serum glucose concentration in dogs is 71-115 mg/dl, but the clinical sings of hypoglycaemia in dogs usually are not manifested until the glucose conctration is less than 50 mg/kg. The second and more restrictive usage of hypoglycaemia, which is used in this report, is to designate a condition in which the glucose concentration is low enough to cause clinical signs (Little, 2005). Differential diagnosis of hypoglycaemia in dogs includes insulinoma, insulin overdose, sepsis, extrapancreatic neoplasia, adrenocortical insufficiency and congenital portosystemic shunts (Murtaugh and Kaplan, 1992). In this dog the results of complete blood count were within normal range, this reduces the possibility of sepsis as a contributing factor in development of persistent hypoglycaemia and sings of weakness and seizure in our case. In this case, we did not perform adrenal function tests. However, hypoglycaemia due to Addison's disease is usually associated with prerenal azotaemia, hperkalaemia, hyponatraemia and hypochloraemia (Reusch, 2000). Our laboratory tests indicated that there were no abnormalities in serum BUN and electrolyte levels.

Hypoglycaemia is frequently recognized as a paraneoplastic syndrome in dogs. Tumour-associated hypoglycaemia has been reported in dogs with pancreatic beta-cell tumours, hepatic tumours, and rarely with other neoplasms such as smooth muscle tumours (jejunal leiomyoma, gastric leiomyoma and leiomyosarcoma) (Beaudry *et al*., 1995). Serum biochemical analysis showed the hepatic variables within reference limits, therefore, hepatic tumour was considered less likely in this dog.

In this dog, history and clinical findings did not indicate the presence of gastrointestinal signs of gastric leiomyoma or jejunal leiomyoma (vomiting, hematemesis, melena or chronic small intestinal diarrhoea). Furthermore, the lack of masses or organomegaly in physical, radiographic and ultrasonographic examinations reduces the possibility of the presence of these abnormalities. Information achieved from the veterinary literature indicated that these smooth muscle tumours are rare causes of paraneoplastic hypoglycaemia (Bellah and Ginn, 1996). In comparison with other causes of tumour-related hypoglycaemia, insulinomas are the most common cause of cancer-associated hypoglycaemia. These tumours are normally diagnosed on the basis of concurrent hypoglycaemia and hyperinsulinaemia, or relative hyperinsulinaemia (Lamb *et al*., 1995). Insulinomas are often very small and difficult to recognize in radiology and ultrasonography, and failure to identify a mass lesion in the region of the pancreas is common (Hackett, 1999; Nelson, 2000). In our case exploratory laparotomy, surgical resection of pancreatic mass in association with histopathological findings resulted in complete resolution of neoplastic hypoglycaemia and confirming the diagnosis of insulinoma. In the cases of canine insulinoma, there is a gradual decline in blood glucose level and the clinical signs are related to neuroglucopenia. These include hypothermia, mental dullness, seizures, weakness, collapse, and muscle fasciculations. Due to compensatory counter-regulatory mechanisms, clinical signs tend to be episodic and last from a few seconds to a few minutes (Vallee, 2003). We observed some of these clinical signs in our case such as intermittent lethargy, weakness and episodic seizures.

Treatment of insulinomas includes

surgical and medical management. The first mode of treatment should be surgical resection of the tumour. However, medical treatment can be used as an adjunctive treatment when clinical signs recur after surgery or as the sole treatment in those animals for which surgery is not elected or recommended (Tobin *et al*., 1999). In the present case, surgical resection of the tumour resulted in complete resolution of previous clinical symptoms. The aim of authors in this report was to raise awareness about the importance of laboratory tests such as measurement of glucose and insulin levels in the cases with signs of episodic weakness and seizures. The insulin:glucose ratio in our case was determined 0.86 (normal ratio, 0.3). Increased ratio of insulin:glucose suggests excessive insulin with low blood glucose. This occurs with an insulinoma or with an overdose of exogenous insulin (Sodikoff, 2001).

References

Beaudry, D; Knapp, DW; Montgomery, T; Sandusky, GS; Morrison, WB and Nelson, RW (1995). Hypoglycemia in four dogs with smooth muscle tumors. J. Vet. Intern. Med., 9: 415-418.

Bellah, JR and Ginn, PE (1996). Gastric leiomyosarcoma associated with hypoglycemia in a dog. J. Am. Anim. Hosp. Assoc., 32: 283-286.

Elie, MS and Zerke, CA (1995). Insulinoma in dogs, cats and ferrets. Compend. Contin. Educ. Pract. Vet., 17: 51-58.

Hackett, T (1999). Hypoglycemia. In: King, L and Hammond, R (Eds.), *BSAVA manual of canine and feline emergency and critical care*. (1st Edn.), United Kingdom, British Small Animal Association. P: 181.

Kenneth, WS and Cook, A (1998). Hypoglycemia. In: Torrance, AG and Mooney, CT (Eds.), *BSAV manual of small animal endocrinology*. (2nd Edn.), United Kingdom, British Small Animal Association. P: 141.

Kraje, AC (2003). Hypoglycemia and irreversible neurologic complications in a cat with insulinoma. J. Am. Vet. Med. Assoc., 223: 810, 812-814.

Lamb, CR; Simpson, KW; Boswood, A and Matthewman, LA (1995). Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases. Vet. Rec., 137: 65-68.

Leifer, CE; Peterson, ME and Matus, RE (1986). Insulin-secreting tumor: diagnosis and medical and surgical management in 55 dogs. J. Am. Vet. Med. Assoc., 188: 60-64.

Little, CJ (2005). Hypoglycaemic bradycardia and circulatory collapse in a dog and a cat. J. Small Anim. Pract., 46: 445-448.

Murtaugh, RJ and Kaplan, PM (1992). *Veterinary emergency and critical care medicine*. 1st Edn., Mosby, St. Louis, Missouri. P: 254.

Nelson, RW (2000). Insulin secreting islet cell neoplasia. In: Ettinger, ST and Feldman, EC (Eds.), *Textbook of veterinary internal medicine. Diseases of the dog and cat*. (5th Edn.), Philadelphia, W. B. Saunders Co., PP: 1429-1438.

Ogilvie, Gk (1996). Tumors of the endocrine system. In: Withrow, SJ and Macedwen, EG (Eds.), *Small animal clinical oncology*. (2nd Edn.), Philadelphia, W. B. Saunders Co., PP: 316-346.

Parker, AJ; Musselman, EM and O'Brien, D (1981). Diazoxide treatment of canine insulinoma. Vet. Rec., 109: 178-179.

Pilny, AA and Chen, S (2004). Ferret insulinoma: diagnosis and treatment. Compend. Contin. Educ. Pract. Vet., 26: 722-729.

Reusch, CE (2000). Hypoadrenocortism. In: Ettinger, ST and Feldman, EC (Eds.), *Textbook of veterinary internal medicine. Diseases of the dog and cat*. (5th. Edn.), Philadelphia, W. B. Saunders Co., PP: 1489-1499.

Sodikoff, CH (2001). *Laboratory profiles of small animal diseases*. 3rd Edn., Mosby, St. Louis, Missouri. P: 49.

Tobin, RL; Nelson, RW; Lucroy, MD; Wooldridge, JD and Feldman, EC (1999). Outcome of surgical versus medical treatment of dogs with beta cell neoplasia: 39 cases (1990-1997). J. Am. Vet. Med. Assoc., 215: 226-230.

Tongson-Ignacio, JE; Honda, SA and Bhagavan, NV (2005). Insulinoma, a rare neuroendocrine tumor: a case report. Hawaii Med. J., 64: 9-11.

Vallee, IK (2003). Insulin-secreting beta cell neoplasia in a 10-year-old dog. Can. Vet. J., 44: 592-594.

Vannevel, JY and Wilcock, B (2005). Insulinoma in 2 guinea pigs (*Cavia porcellus*). Can. Vet. J., 46: 339-341.