

## Insulinoma in a dog; case report

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### ABSTRACT

A case of an 8-year-old female Irish Setter is described. The animal was presented at the Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, with a history of episodic seizures. Based on a high insulin concentration (316.64 pmol/l) and the concurrent presence of severe hypoglycaemia (1.8 mmol/l) a diagnosis of pancreatic beta cells tumour, or insulinoma, was postulated. Therapy was unsuccessful and after three weeks the owners decided to euthanise the dog. Necropsy revealed a right pancreatic lobe tumor that was pathohistologically confirmed as beta cell tumor, or insulinoma.

**Key words:** insulinoma, clinical findings, pathological findings, dog

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## Introduction

Pancreatic insulin-secreting tumors are also known as insulinomas or beta cell tumors. These tumors are uncommon in the dog and extremely rare in other domestic animals. They generally occur in middle-aged to older dogs (mean age 9 years) with no sex predilection. The most common breeds affected include boxers, German Shepherds, Irish Setters, standard poodles, collies, Labrador Retrievers, and fox terriers (OGILVIE, 1996).

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Insulinomas, as a functioning tumors of the beta cells of the pancreatic islets, secrete inappropriately high amounts of insulin. In the normal animal, insulin secretion is regulated by serum glucose concentrations; as blood glucose concentrations increase postprandially, insulin secretion also increases, which subsequently decreases serum glucose concentrations by promoting glucose uptake by peripheral tissues and liver glycogenesis. In the presence of an insulinoma, insulin secretion is unresponsive to the regulating effect of serum glucose concentrations, and the tumor will continue to overproduce insulin in the presence of hypoglycaemia. Clinical signs of this tumour are a result of hypoglycaemia, which causes neuroglycopenia and stimulation of the sympathetic nervous system, which results in elevated circulating catecholamine concentrations. These clinical signs are usually episodic and include seizures, weakness, collapse, ataxia, posterior paresis, muscle fasciculations, dementia and depression. Obesity, owing to the anabolic effects of insulin and neurologic abnormalities are the most common findings (WATERS and SCOTT-MONCRIEFF, 1998)

The aim of this paper is to present the first described case of this rare tumor in a dog in Croatia.

## **Materials and methods**

### *Clinical examination*

An 8-year-old female Irish Setter was presented at the Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb and was fully clinically examined, which also included neurological and laboratory examinations.

### *Laboratory*

Blood samples were taken and a biochemical analysis was performed after centrifugation at 1200 g for ten minutes. Glucose, insulin, serum amylase, alanine aminotransferase (ALT), blood urea nitrogen (BUN) and creatinine levels were measured. Glucose, serum amylase, ALT, BUN and creatinine were determined using biochemical autoanalyser Technicon RA 1000, Tarrytown, New York. Reagents were supplied by Randox. Insulin was determined using the RIA method.

### *Necropsy*

Necropsy was performed following euthanasia with Thiopental (natrium-5-aethyl-5-/1-methyl-butyl/-2-thiobarbituricum, produced by

SPOFA, United Pharmaceutical Works, Prague, Czech Republic). Tissues for pathohistological examination (pancreas, liver and brain) were fixed in neutral buffered formalin, embedded in paraffin. Following deparaffinisation they were stained using the haematoxylin-eosin method. Pancreatic tissue was also immuno-histochemically stained with insulin monoclonal antibodies using the avidine-biotin-complex method and LSAB diagnostic kits. All reagents were supplied by DAKO (Glostrup, Denmark).

## Results

The studied animal was presented with a history of progredient seizures which at the time of arrival were occurring several times daily. Seizures had started two months previously, predominantly after some physical activity. The owners noticed that application of honey into the oral cavity significantly reduced the duration of the seizure. Thus, immediately upon arrival, blood glucose level was 12 mmol/l (referent range 3.5 – 5.5 mmol/l according to: TORRANCE and MOONEY, 1998) and neurological examination revealed no abnormalities. However, after one hour the seizures recurred, and in the second blood sample the blood glucose level dropped to 1.8 mmol/l. From the same sample, insulin level was determined at the time of hypoglycaemia. Insulin level was extremely high – 316.64 pmol/l. Based on that data, pancreatic insulinoma was diagnosed. The owners were advised to feed the animal very frequently to prevent hypoglycaemic episodes. After three weeks the animal's condition deteriorated and oral therapy with prednisolone (2 mg/kg body mass) was

Table 1. Some blood biochemistry values in a 8-year-old female Irish setter dog with an insulinoma

Serum biochemistry	Value	(TORRANCE and MOONEY, 1998)
Insulin (pmol/l)	316.64	36-144
BUN (mmol/l)	6.2	3-9
Creatinine ( $\mu$ mol/l)	92	20-110
ALT (U/l)	22	<100
Serum amylase (U/l)	1480	400-2000

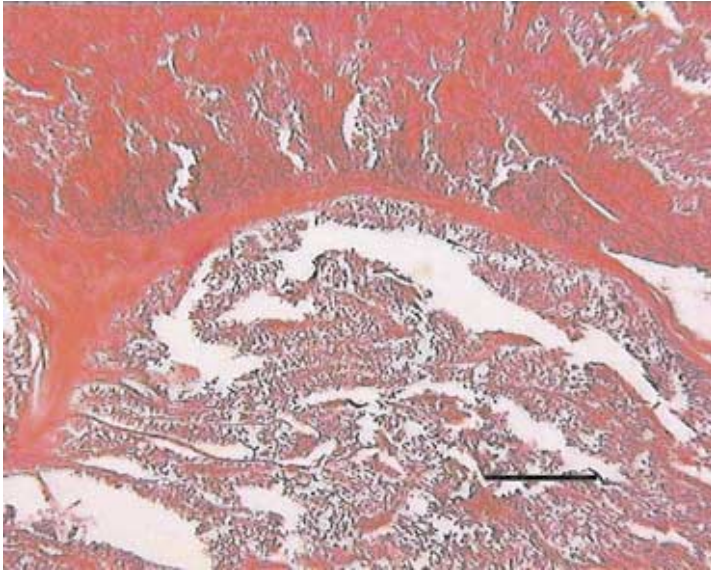


Fig. 1. Islet-cell tumor in a dog pancreas with dense fibrous strands and tumour cells arranged in cords. HE;  $6.3\times 10$ ; scale bar =  $150\ \mu\text{m}$ .

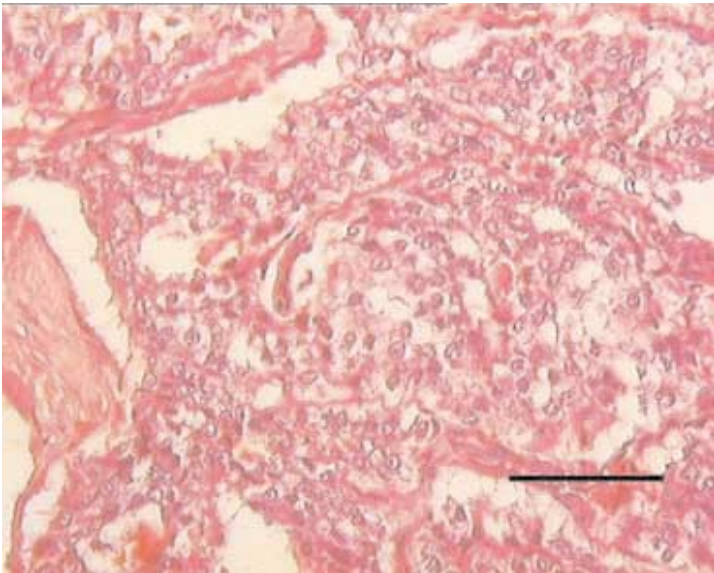


Fig. 2. Islet-cell tumor in a dog pancreas with discrete lobular pattern. HE;  $40\times 10$ ; scale bar =  $40\ \mu\text{m}$ .

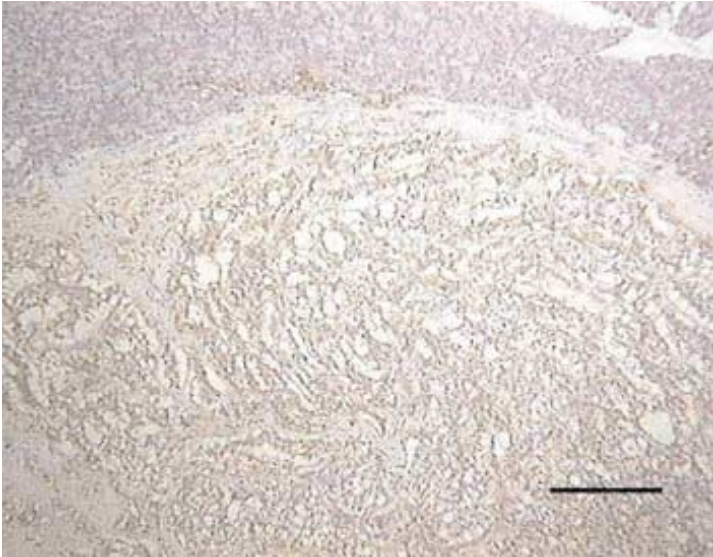


Fig. 3. Immunohistochemical insulin staining in a dog pancreas. The lower part of the picture shows positive stained (brown colour) tumor. ABC immuno-staining;  $6.3\times 10$ ; scale bar =  $150\ \mu\text{m}$ .

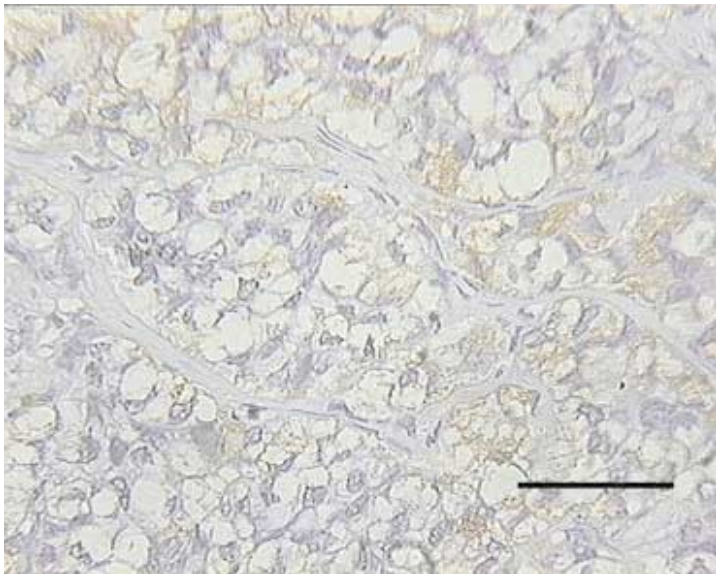


Fig. 4. Detail of Fig. 3 with heavily vacuolated insulin positive tumor cells in a dog pancreas.  $40\times 10$ ; scale bar =  $40\ \mu\text{m}$ .

introduced. However, prednisolone therapy did not result in any clinical improvement and the owners decided to euthanise the animal.

Necropsy revealed several indurate oval grey white masses with an average size of 1.5 cm randomly scattered throughout the right pancreatic lobule. The liver was slightly enlarged and congested. General congestion due to barbiturate euthanasia was noticed. Pathohistological examination of the pancreas revealed a pancreatic islet-cell tumor encapsulated with abundant strands of connective tissue stroma separating the tumour cells into lobules and cords. The nuclei were oval, often vesicular with prominent nucleoli. Mitotic figures were infrequent. The cytoplasm of the tumor cells predominantly contained large vacuoles (Figs. 1 and 2). The other tumor cells contained granular eosinophilic or basophilic material. Immunohistochemical staining showed strong positive insulin reactivity in the majority of the tumor cells (Figs. 3 and 4). Liver pathohistological examination revealed non-specific hydropic changes, and the brain tissue (cerebrum and cerebellum) was without noticeable change, except for congestion.

## Discussion

Diagnosis of an insulinoma can be made clinically only through determination of blood glucose and, in the same sample, insulin level. If there is hypoglycaemia and hyperinsulinaemia with an insulin concentration above 144 pmol/l, such a finding is consistent with insulinoma (TORRANCE and MONEY, 1998). In this case these biochemical values were wholly present. In the literature there are much partially controversial data which are oriented to clinical evaluation of the insulin:glucose ratio (IGR) and amended insulin:glucose ratio (AIGR) (KNOWLEN and SCHALL, 1984; EDWARDS, 1986; THOMPSON et al., 1995), which is calculated as follows:

$$AIGR = \frac{\text{plasma insulin ( IU / ml ) } 100}{\text{plasma glucos e ( mg / dl ) } 30}$$

The AIGR is based on the assumption that insulin levels should be zero if blood glucose falls below 30 mg/dl. It is generally accepted that an AIGR greater than 30 is consistent with an insulinoma. However, this calculation is used in possible cases of this tumor and it is not performed if the above-mentioned hyperinsulinaemia exists. Merely for the record, in our case AIGR was 1594.67.

Our pathological findings are consistent with literature data (CAPEN and MARTIN, 1969; STRAFUSS et al., 1971; MATTHEUWS et al., 1976; CAYWOOD et al., 1979; HUXTABLE and FARROW, 1979; PRESCOTT and THOMPSON, 1980; DAHLGREN and EMERICK, 1985; LEIFER et al., 1985; COX, 1999). Based on that, and especially upon on the positive immunohistochemical staining for insulin, it may be concluded that in this case the tumor was adenoma of the pancreatic beta cells. In the literature, both functional adenomas and adenocarcinomas are described (CAPEN and MARTIN, 1969; CAPEN, 1995), but the prognosis is generally poor and depends on the tumor stage (OGILVIE, 1996; WATERS and SCOTT-MONCRIEFF, 1998). However, most insulinomas in dogs are adenocarcinomas, which can be divided into three stages: Stage I – tumor cells only in pancreas; Stage II – tumor cells in the pancreas and regional lymph nodes; Stage III – tumor cells in distinct metastatic sites (MCDERMOTT et al., 1999).

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**SAŽETAK**

U radu je opisan inzulinom u osmogodišnje kuje, pasmine irski seter. Vlasnici su životinju doveli na pregled u Kliniku za unutarnje bolesti Veterinarskog fakulteta u Zagrebu zbog povremenih epileptiformnih napada. Temeljem analize poremećaja u koncentraciji inzulina (316,64 pmol/l) koja je bila znatno povećana u istodobnoj nazočnosti hipoglikemije (1,8 mmol/l), postavljena je dijagnoza tumora beta stanica gušterače ili inzulinoma. S obzirom da terapija nije bila uspješna, vlasnici su se odlučili za eutanaziju. Razudbom je utvrđen tumor desnog reznja gušterače za koji je patološkohistološkom pretragom dokazano da se radi o inzulinomu.

**Ključne riječi:** inzulinom, klinički nalazi, patološki nalazi, pas

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