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Juvenile diabetes mellitus with exocrine pancreatic insufficiency in a Thai Bangkaew dog: a case report

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Case Report

Juvenile diabetes mellitus with exocrine pancreatic insufficiency in a Thai Bangkaew dog: a case report

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Abstract

An 8-month-old intact male Thai Bangkaew bred dog presented with polyuria, polydipsia, polyphagia, exercise intolerance and weight loss over 2 weeks. The serum biochemistry profiles revealed hyperglycemia, glycosuria and high serum fructosamine concentrations indicating the development of diabetes mellitus. The dog had a good response to a half-dose of intermediate-insulin injection twice daily monitored by the improvement of clinical signs and serum fructosamine. This was supposed to be due to the partial destruction of islets of Langerhans. Two months later, voluminous diarrhea with greasy stools, dry coat hair and generalized alopecia were observed. However, the clinical signs of diabetes mellitus, such as polyuria and polydipsia were not noticed. The levels of canine-trypsin-like immune-reactivity and cobalamin were below the normal range. This suggested exocrine pancreas loss of function. To determine the etiology, serum insulin was measured revealing a very low level. On the other hand, serum canine pancreas-specific lipase and C-reactive protein were in the normal range. Using ultrasonography, immune-mediated pancreatic fibrosis was suspected while pancreatitis was a lesser possibility. Successful treatment was achieved with a combination of low-dose insulin, pancreatic enzymes and methylcobalamin promoting weight gain and exercise tolerance. This case was a report of juvenile diabetes mellitus concurrent with exocrine pancreatic insufficiency in a Thai Bangkaew dog, which had not been well recognized. Additional to the Thai Bangkaew breed, this report might be an important piece of scientific knowledge that might be of potential hereditability and economic importance in the future.

Keywords: diabetes mellitus, exocrine pancreatic insufficiency, juvenile, Thai Bangkaew

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Introduction

The pancreas has two main functions, endocrine and exocrine. Clusters of endocrine pancreas cells are called islets of Langerhans which regulate the blood glucose level. The destruction of β-cells in islets of Langerhans leads to insulin deficiency causing insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes mellitus (type 1 DM) characterized by hyperglycemia which is a common endocrine disease in middle age or older age (Gilor *et al.,* 2016). Lack of insulin leads to abnormal metabolism of carbohydrate, fat, and protein, and increase catabolism causing polyuria (PU), polydipsia (PD), polyphagia (PP), and weight loss (Behrend *et al*., 2018).

In addition to endocrine function, the pancreas produces enzymes important for food digestion. Loss of exocrine glands result in mal-digestion, the incomplete breakdown of nutrients, known as exocrine pancreatic insufficiency (EPI) determined by low canine trypsin-like immune-reactivity (TLI). Polyphagia (PP), weight loss, and steatorrhea are the most common clinical signs, which are usually related to pancreatic acinar atrophy (PAA), reported in dogs between 6 months to 6 years old. Chronic pancreatitis, repeated episodes of acute or subacute pancreatitis, and pancreatic hypoplasia, a rare congenital condition, are also the causes that affect synthesis and secretion of digestive enzymes by exocrine portion of the pancreas (Hall 2003; Rallis and Adamama-Moraitou 2004).

In the last decade, DM concurrent with developing EPI in dogs, caused by chronic pancreatitis, has become more apparent (Watson 2003; Davison 2015) but cases are rare in dogs of less than one year old. Puppies suffer from endocrine and exocrine pancreatic insufficiency associated with immune-mediated disease, which had been reported in German Shepherds, Greyhounds, Golden Retrievers Labrador Retrievers and crossbred dog disease is commonly noticed (Niger 1996; Mamom and Rungpupradit 2010; Alvarez *et al*., 2016; Anton *et al*., 2020).

The Thai Bangkaew dog (TBD) is a Spitz type working dog, categorized by Federation Cynologique Internationale (FCI), that originated in central Thailand. In clinical practice, veterinarians have found that Thai Bangkaew dogs suffer from common diseases, including of the gastrointestinal tract and accessory organs. However, there is no scientific data that has been reported about pancreatic diseases, especially in the younger age. Moreover, the common diseases and breed predisposition are still limited data in the Thai Bangkaew breed. Only one scientific report has shown a dog suffering from adenocarcinoma at trigone of urinary bladder (Samujit 2018). Here, we report a case of juvenile diabetes mellitus (DM) concurrent with exocrine pancreatic insufficiency (EPI) in a Thai Bangkaew dog from Thailand.

Clinical description

An 8-month-old, 13.8 kg intact male Thai Bangkaew dog was presented to a private primary care hospital for polyuria (PU), polydipsia (PD), polyphagia, exercise intolerance and weight loss of 1 kg over two weeks. However, this dog was still alert, responsive and had a good appetite without a history of gastrointestinal signs such as abdominal pain, vomit and diarrhea. The dog had already received a necessary health program, consisting of vaccination, de-worming and ectoparasite control. A physical examination revealed an abnormality in that the dog had a body condition score (BCS) of 1.5 /5 and 5% dehydration. No abdominal pain was observed. As shown in the Table 1, a complete blood count (CBC) presented thrombocytopenia (166 x 10^3 cell/mm^3, reference interval [RI] 200-500 x 10^3 cell/mm^3), and fresh blood smear found *Ehrlichia canis*. Serum biochemistry panels revealed hyperglycemia (325 mg%, RI 80-120 mg%) and high fructosamine levels (622 umol/L, RI 170-338 umol/L) (Table 2). Urinalysis showed glucosuria (2+) without ketonuria (Table 3). Canine pancreas-specific lipase using Vcheck cPL was 50 ng/ml (RI 0-199 mg/ml) and ultrasonography revealed that the pancreas had mild heterogenous parenchyma but was unremarkable in size and shape (Fig 1a). This suggested that pancreatitis might not be the main concern. According to laboratory results, the final diagnosis in this case was diabetes mellitus (DM) and ehrlichiosis. For controlling hyperglycemia, 0.25 IU/kg of intermediate-acting insulin (caninsulin®) every 12 hours was designed for use together with a low-glycemic diet and subcutaneous fluids. 10 mg/kg of doxycycline once daily for 30 days was planned to treat *E.canis* infection. After starting treatment, this dog was well recovered from illness detected by clinical signs. PU/PD ceased within a few days, then weight gain and exercise tolerance were obviously observed in two weeks. Normal hematological profiles with no blood parasite were reported within one month. However, hypoglycemia (50 mg%, RI 80-120 mg%) was detected after giving to the dog for one week a half-dose of caninsulin® (0.12 IU/kg) twice daily, designed to treat DM.

Two months later, the dog was well recovered, including no PU/PD, weight gain with BSC of 2/5, exercise tolerance and no hypoglycemia. However, this dog had diarrhea with fecal score of 5/7 and voluminous and pale colored stools. Dry coat hair and generalized alopecia were also observed. Blood tests showed that serum fructosamine level had decreased compared to the previous test (488 umol/L, RI 170-338 umol/L). This indicated that the blood glucose control was progressing with good efficacy. To determine the type of DM in this case, the analysis of fasting serum insulin level was performed and the result showed a low level of serum insulin (1 µIU/ml, RI 8.1-31.9 µIU/ml) suggesting that this dog was most affected by type 1 DM. Other basic blood profiles and inflammation marker, C-reactive protein (CRP), were in normal range. The analysis of intestinal function was analyzed and hypocobalaminemia with normal folate levels were shown. In addition to diagnostic tests, the exocrine pancreatic function was determined using canine-trypsin-like immunoreactivity (cTLI). The result showed a low serum level (1.87 ng/ml, RI 5-35 ng/ml), which indicated that exocrine pancreas was unable to produce the digestive enzymes for food digestion. The ultrasonography revealed heterogenous hyperechoic parenchyma of pancreas compared to the previous study. No sign of inflammation of the surrounding pancreatic fat (Figure 1b). These findings

suggested that pancreatic fibrosis without pancreatitis was highly suspected.

Hence, this dog had a loss of two main pancreatic functions, including endocrine and exocrine, causing diabetes mellitus and exocrine pancreatic insufficiency. Therefore, commercial pancreatic enzymes (Lypex®) and 500 mg of oral methylcobalamin were added to the treatment each day. Because the clinical signs of DM were not detectable and the average nadir was 128±29 mg% which was in acceptable range (80-150 mg%) (Figure 2), the half-dose of caninsulin® (0.12 IU/kg) was also continued. Ordinary commercial diet was preferred to feed than high fiber diet because of the low ability of digestion in this case. Following the management, small bowel diarrhea was resolved in a few days. BCS increased to 3/5 with 15.3 kg body weight and skin conditions improved, such as no alopecia and scaling in a few weeks. One month after treatment of EPI, the dose of insulin was increased to 0.15 IU/kg twice daily because the presenting of PU/PD was observed.

Table 1 Hemogram

Parameter	Unit	Reference value (Latimer *et. al.*, 2011)	Day 1	Month 1	Month 2
Red blood cell (RBC)	Cell/mm^3	5.5-8.5 x10^6	6.96	5.99	6.31
Hemoglobin	g/dl	12.0-18.0	14.6	12.6	13.6
Packed cell volume (PCV)	%	37-55	42.7	37.6	38
Indices MCV	fl	60-77	61.3	62.7	60.2
MCH	pg	20-25	20.9	21.1	21.5
MCHC	g/dl	32-36	34.1	33.71	32.7
RDW	%	12-15	13.7	13.8	13.1
WBC	cell/mm^3	6,000-17,000	11,100	8,300	10,800
Neutrophil		3000-11500	6,993	5,063	7,668
Band		300	0	0	0
Lymphocyte		1000-4800	3,330	2,407	2,376
Monocyte		150-1350	222	332	216
Eosionophil		100-1250	5	6	5
Basophil		<100	0	0	0
Platelet	cell/mm^3	200-500 x10^3	166	216	225
Blood Parasite			*E.canis*	Not found	Not found

MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration, RDW: red cell distribution width; WBC: White blood cell

Table 2 Serum biochemistry profiles

Parameter	Unit	Reference value (Latimer *et. al.*, 2011)	Day 1	Month 1	Month 2
BUN	mg/dl	7-27	14	18	1.6
Creatinine	mg/dl	0.5-1.5	1.27	1.36	1.19
SDMA	µg/dl	0-14	-	8	-
AST	U/L	0-50	42	39	-
ALT	U/L	10-100	42	41	-
ALP	U/L	20-120	50	41	-
Albumin	g/dl	2.7-4.2	-	-	3
Cholesterol	mg/dl	125-300	-	-	277
Triglyceride	mg/dl	20-200	-	-	131
Blood glucose	mg%	80-120	392	235	262
Fructosamine	µmol/L	170-338	622	426	488
cPL (V-check)	ng/ml	0-199	50	-	-
C-reactive protein	mg/L	0-19	-	-	10
C-TLI	ng/ml	5-35	-	-	1.87
Serum folate	µg/L	7.7-24.4	-	-	9.9
Serum cobalamin	ng/L	226-661	-	-	204
Insulin	µlU/ml	8.1-31.9	-	-	1

BUN: Blood urea nitrogen; SDMA: Symmetric dimethylarginine; AST: Aspartate transaminase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; cPL: Canine pancreas-specific lipase; C-TLI: Canine-trypsin-like Immunoreactivity

Table 3 Urinalysis results

Parameter	Reference value (Latimer *et. al.*, 2011)	Day 1	Month 1
Source		Catheterization	Voiding
Color		Pale yellow	yellow
Transparency		Slightly Turbid	Clear
Chemical examination			
pH	5.2-6.8	6.5	5.5
SG	1.015-1.045	1.035	1.041
Protein	Neg	2+	Neg
Glucose	Neg	2+	2+
Ketone	Neg	Neg	Neg
Blood	Neg	1+	Neg
Bilirubin	Neg	Neg	Neg
Leukocyte	Neg	Neg	Neg
Nitrite	Neg	Neg	Neg
Urobilinogen	Neg	Normal	Normal
Microalbumin	Neg	Neg	Neg
Microscopic examination			
WBC	0-5 /HPF	-	1-2/HPF
RBC	2-3 /HPF	3-5 /HPF	-
Epithelial cell	0-1 /HPF	0-1/HPF	-
Bacteria		Few (Cocci)	Few (Cocci)

pH: Blood urea nitrogen; SG: Specific gravity; WBC: White blood cell; RBC: Red blood cell; Neg: negative; HPF: High-power field

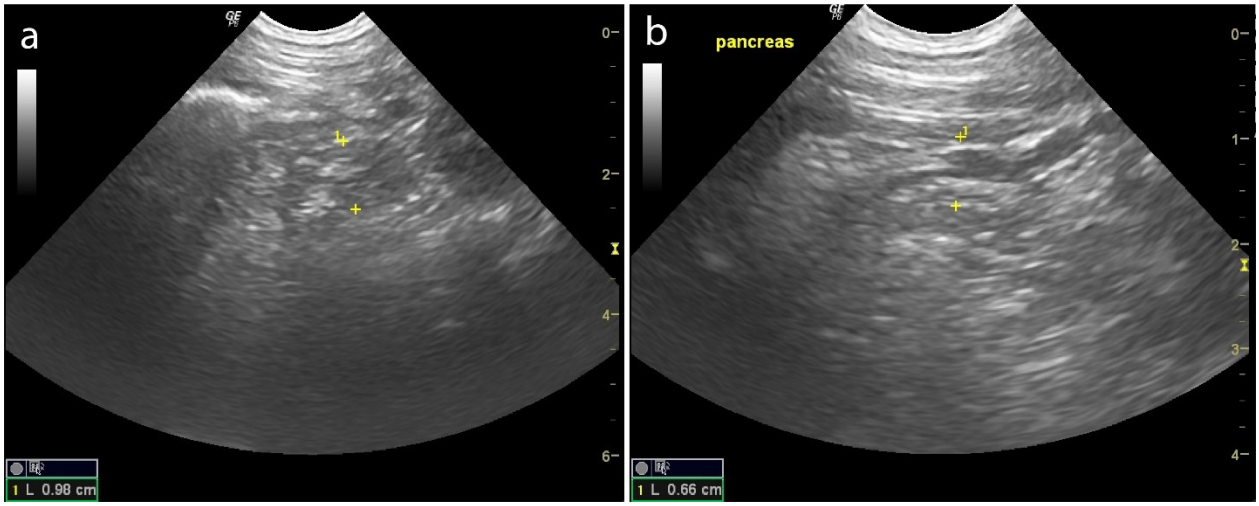

Figure 1 The ultrasonography of pancreas. a, heterogenous parenchyma with unremarkable of size and shape. b, heterogenous hyperechoic parenchyma compared to the previous study and no sign of inflammation of surrounding pancreatic fat.

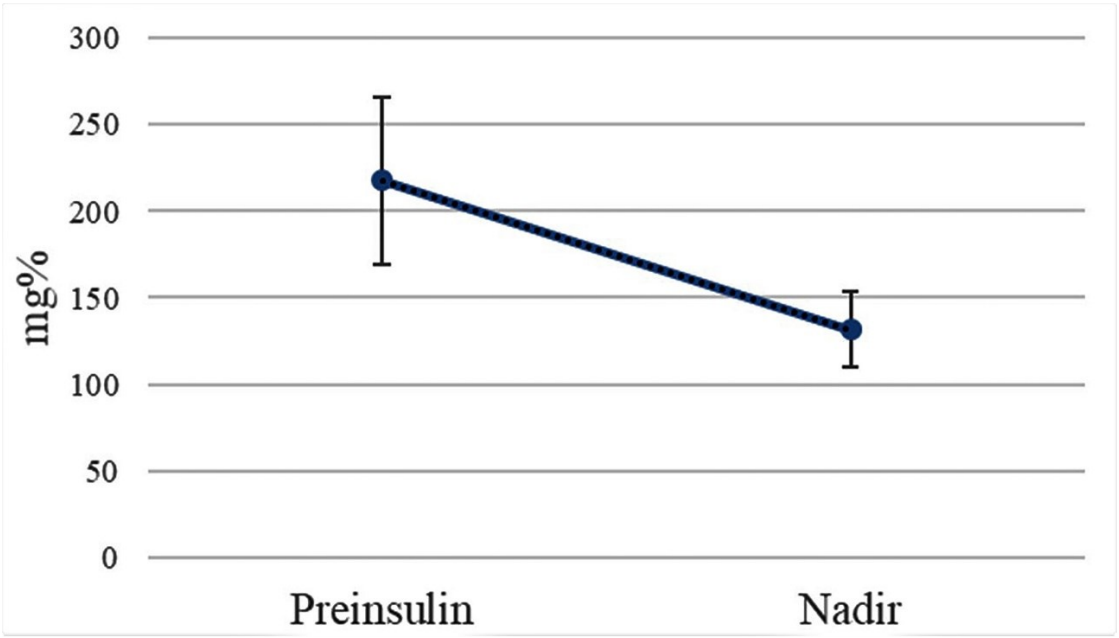

Figure 2 Average blood glucose monitoring of pre-insulin and nadir during the first 3 months of the treatment.

Discussion

Canine juvenile DM, which is diagnosed in young animals less than six months of age, describes insulin-dependent dogs with various histopathologic abnormalities of the pancreas, but no clear etiology (Kang *et al.,* 2008; Gilor *et al.,* 2016). These are considered to be congenital in origin known as β-cell specific including hypoplasia/abiotrophy, in the absence of EPI (Atkins *et al.,* 1988). The autoimmune disease in a 3-month-old male Donge de Bordeaux dog was also the etiology of DM in which the massive lymphocytic infiltration associated with decreased and lost endocrine led to lymphocytic insulitis and a severe atrophy of the islets of Langerhans (Jouvion *et al.,* 2006; Davison 2015).

For exocrine pancreatic disease, dogs with EPI attributes to pancreatic acinar atrophy (PAA) are typically young adults (1–2 years of age). On the other hand, dogs with EPI due to chronic pancreatitis are often middle-aged to older but can be of any age (Cyrus and Stainer, 2011). The atrophy of pancreatic acinar is most commonly found in young German Shepherd dogs and rough-coated Collies, although the prevalence of both is estimated at 1%. Using histopathologic and etiopathogenetic study it was revealed that these two breeds suffered from an inherited condition, autoimmune-mediated atrophic lymphocytic pancreatitis described by pathological findings (Wiberg 2003).

There have been a few reports of DM accompanied by EPI in a 3-month-old female Labrador Retriever and a German shepherd which presented with polyuria, polydipsia, polyphagia, diarrhea and emaciation (Niger *et al.,* 1996; Kang *et al.,* 2008; Alvarez *et al.,* 2015). Additionally, a young Golden Retriever and 12 Greyhounds suffered from Juvenile pancreatic acinar atrophy (PAA) and two of these puppies were described with concurrent endocrine and exocrine failure affected by lymphocytic or lymphoplasmacytic pancreatitis after necropsy, however, no acute pancreatitis signs such as pain and vomiting were observed (Brenner *et al.,* 2009, Mamom and Rungpupredit 2010). Recently, juvenile DM type 1 and that EPI and hypothyroidism occurred simultaneously in 5-month-old crossbred dog exhibiting not only typical signs of both pancreatic diseases but growth retardation, associated with the small values of insulin-like growth factor I and serum insulin, was observed (Anton *et al*., 2020).

In our case, the age of the dog was slightly older than previous reports which were of an average of 3 months old, furthermore, the dog had normal growth together with a history. Up until 8 months old, this dog obviously presented typical signs of DM such as PU/PD/PP caused by hyperglycemia and glycosuria, but still had a normal fecal score and normal defecation frequency. As a result, canine juvenile DM was diagnosed. According to reports of DM in puppies, insulin-dependent dogs were mostly determined. Type 1 DM was also diagnosed in our case, detected by a low serum insulin level and ultrasound imaging. Treated with intermediated-acting insulin, the dog had a good response to a half-dose insulin injection, this was presumably due to the existence of β-cell residual function called the honeymoon period (Abdul-Rasoul *et al.,* 2006 and Gilor *et al.,* 2016). Therefore, clinical signs and blood glucose should be monitored and the dose of insulin should be adjusted in the future. Two months later, the loss of exocrine function was detected by low TLI level and dog showed small bowel diarrhea with greasy stools. This indicated that the destruction of pancreatic tissue was progressive.

Canine Ehrlichiosis is a gram negative obligate intracellular bacterium, which is known to cause a multisystemic disease widespread throughout the different body systems with the potential to cause various clinical signs. Histopathological findings have revealed lymphocytic, plasmacytic and monocytic infiltrations and perivascular cuffing in numerous organs including the central nervous system, eyes, lymph nodes, spleen, liver, kidneys, urinary bladder, pancreas, prostate and testes. Immune-mediated mechanisms have been suggested as a role in the pathogenesis leading to vasculitis, glomerulonephritis, hepatitis, meningoencephalitis, lymphocytic infiltration of the nervous system or hemorrhages. (Harrus *et al*., 2001; Baneth 2006; Unvera *et al*., 2009; Waner and Harrus 2013). The pathological change of pancreas has not been commonly reported, while the effects of ehrlichiosis in pancreatic functions were already determined. 20% of *E.canis*-infected dogs revealed the increased serum cPLI concentration consistent with mild and clinically non-apparent pancreatic inflammation that may occasionally be a pathogenetic component of this pathogen (Mylonakis *et al.,* 2014). *E.canis* also induces an impaired glucose tolerance and higher levels of serum insulin than normal value that indicates subclinical type II DM but the pathogenesis has not clearly been established (Deepa *et. al*., 2014). In contrast to the above mentioned, cPL and CRP concentration levels of our dog were in normal range together with no active inflammation in pancreas using ultrasonography. This suggested that the active inflammation of pancreas was not observed at the time of diagnosis, although, the previous active inflammation-induced pancreatic function abnormality could not be determined. Doxycycline is very efficient in clearing *E.canis* infection and the resolution of clinical signs, hematological and biochemical abnormalities generally take within 3 weeks (Mylonakis *et al.,* 2010; Mylonakis *et al.,* 2019). In this case report, the dog had not presented any signs of ehrlichiosis excepting thrombocytopenia, which was resolved within one month after doxycycline administration. However, signs of DM were still progressing after a complete treatment of *E.canis* infection and the EPI had consequently manifested in two months indicating persistent pancreatic destruction. Endocrine and exocrine pancreatic insufficiency-associated ehrlichiosis had still lacked scientific evidence and the persistent DM and/ or EPI secondary to *E.canis* infection had not obviously been described. In this report, the authors cannot rule out that ehrlichiosis inducing permanent damage of the pancreas, although, it might be a lesser possibility. Therefore, histopathology and DNA sequence from pancreas tissue should be investigated.

As in the above discussion, juvenile DM combined by EPI resulted from pancreatic hypoplasia or immune

mediated-pancreatic atrophy which are commonly detected in decreased pancreatic size using non-invasive imaging (Rajapakshage *et al.*, 2016). In this case, ultrasonography revealed a normal size and shape of pancreas with heterogenous parenchyma without inflammation of the surrounding pancreatic fat was observed at first time diagnosis, and then pancreatic fibrosis likely developed a few month later. From these findings, the pancreas was probably in early to mid-stage of immune mediated-pancreatic atrophy but was not a congenital hypoplasia evaluated by decreased pancreatic size after birth. In case of immune-associated disease, low numbers of pancreatic acinar cells and islets were described in young dogs with exocrine and endocrine insufficiency (Watson 2003; Brenner *et al.*, 2009). Therefore, coincidences between DM and EPI in this dog might be due to simultaneous damage of exocrine and endocrine pancreatic tissue. To confirm the speculation, pancreatic tissue biopsy should be performed on this dog.

In conclusion, this case report described canine juvenile DM concurrent with exocrine pancreatic insufficiency that was uncommon in young age and this disease was not well recognized in Thai Bangkaew dogs. Since the Thai Bangkaew breed was accepted by FCI, the specific congenital or hereditary health problems, which were of economic importance to dog breeders for producing healthy purebred puppies, had not obviously been identified. Hence, these disorders of the pancreas should be considered by veterinarians. Finally, this report might be an important piece of scientific knowledge, associated with heritability, that should be investigated with reference to etiology and pathogenesis in the future.

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