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NOTE

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Relationship between anti-insulin antibody production and severe insulin resistance in a diabetic cat

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ABSTRACT. A 5-year-old castrated male domestic shorthair cat was diagnosed with diabetic ketoacidosis and severe insulin resistance. Although the conventional treatment for diabetic ketoacidosis was provided, the cat required frequent hospitalization because of severe dehydration and repeated diabetic ketoacidosis. We detected anti-insulin antibodies for human in this cat. Serum insulin-binding IgG levels were markedly elevated compared with those in healthy cats and other diabetic cats. We initiated prednisolone to suppress the effects of anti-insulin antibodies. After initiation of prednisolone, the cat was gradually recovered with increasing activity and appetite. Furthermore, satisfactory glycemic control was achieved with combined subcutaneous injection of insulin detemir and insulin degludec.

KEY WORDS: anti-insulin antibody, feline diabetes, insulin degludec, insulin detemir, insulin resistance

Diabetes mellitus (DM) is a common disease encountered in feline medicine. Common causes of feline diabetes include obesity, pancreatic amyloidosis, pancreatitis, hyperadrenocorticism, acromegaly, and pregnancy/diestrus [1, 4, 13, 14]. Feline insulin resistance is defined as persistent serum hyperglycemia despite adequate insulin injection dose (>1.5 IU/kg) [14]. The most severe insulin resistance is found in diabetic cats with concurrent acromegaly and/or hyperadrenocorticism [14]. In human medicine, one cause of poor glycemic control with severe insulin resistance is the presence of anti-insulin antibodies (AIAs) against insulin preparations [5, 15, 23]. However, there have been no reports of a clinical impact, such as insulin resistance, due to AIAs in diabetic cats [14]. In the current report, AIAs were suspected to be the cause of severe insulin resistance in a diabetic cat. The cat was subsequently treated with prednisolone and a combination of insulin detemir and insulin degludec.

A 5-year-old castrated male domestic shorthair cat was presented to the local veterinary hospital with diabetic ketoacidosis. The cat was conscious at the time, with a body weight of 4.6 kg (body condition score 4/9), serious dehydration (8–9%), and a body temperature of 33.8°C. We performed complete blood counts, venous blood-gas analysis, urinalysis, and serum biochemistry (Table 1). Thorax and abdominal radiographic and ultrasound examination revealed pleural effusion, diffuse pulmonary edema, left atrium enlargement, mitral valve regurgitation, and no abnormality in abdominal organs.

Initial treatment consisted of infusion of physiological saline (4 ml/kg/hr), regular human insulin (regular insulin; 0.1 IU/kg/hr), furosemide (1 mg/kg, once), dobutamine (5 µg/kg/min), piperacillin (30 mg/kg, q8hr), and carperitide (0.05 µg/kg/min) for improving pulmonary edema and metabolic acidosis (pH, 7.04). By day 2, pulmonary edema decreased, and glycemic status improved to 106–293 mg/dl. The cat's appetite gradually improved after treating the ketoacidosis, and on day 5 we initiated subcutaneous injection of insulin glargine (0.11 IU/kg, q12 hr), intravenous infusion of regular insulin (0.014 IU/kg/hr), and spontaneous feeding (ROYAL CANIN™ Male Care, 107 kcal/head, q12 hr).

On day 6, intravenous infusion of regular insulin was discontinued, and subcutaneous injection of insulin glargine was increased to 0.24 IU/kg (q12 hr). However, on day 7, the daily blood glucose concentration was 301–564 mg/dl, indicating hyperglycemia. Therefore, on day 8, insulin glargine was replaced with insulin detemir.

On day 15, we adjusted the dose of insulin detemir to 0.5 IU/kg (q12 hr) and achieved acceptable glycemic control (daily glucose concentration of 63–353 mg/dl). The cat was therefore discharged from the local veterinary hospital. However, because

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Table 1. Results of complete blood cell count, venous blood gas analysis, urinalysis, and serum biochemical analysis on days 1, 35, 43, 86, and 282

	Unit	Day 1	Day 35	Day 43	Day 86	Day 282	Reference range
Complete blood cell count							
Red blood cells	$\times10^4/\mu l$	862	734	423	894	799	550–1,000
Hemoglobin (mmol/l)	mmol/l	18.2	13.1	6.5	14.2	11.6	8.0–14.0
Hematocrit	%	40.9	35.5	20.3	43.3	35.6	24–45
MCV	fl	47.4	48.4	48	48.4	44.6	40–55
MCHC	g/dl	44.5	36.9	32.0	32.8	32.6	30–36
White blood cells	$\times10^2/\mu l$	166	232	244	75	48	60–180
Plate	$\times10^4/\mu l$	19.3	46.3	125	50.3	37.9	30–80
Venous blood gases analysis							
pH	–	7.04	7.01	7.43	ND	ND	7.35–7.45
$PvCO_2$	mmHg	36.7	18.6	35	ND	ND	35–45
Sodium	mmol/l	140.7	162.7	164	ND	ND	147.0–156.0
Potassium	mmol/l	3.36	4.27	5.2	ND	ND	3.4–4.6
Chloride	mmol/l	102.3	119.6	130	ND	ND	107–120
Ionized calcium	mmol/l	2.32	2.52	2.78	ND	ND	2.2–2.8
Lactate	mmol/l	0.8	1.4	1.4	ND	ND	0–3
HCO_3^-	mmol/l	9.5	4.4	23.2	ND	ND	20.8–24.2
Urinalysis							
Urine specific gravity	–	1.020	1.040	ND	ND	ND	>1.035
pH	–	5	5	ND	ND	ND	5.5–7.5
Protein	mg/dl	30	30	ND	ND	ND	Below30
Glucose	mg/dl	1,000	1,000	ND	ND	ND	0
Ketones	mg/dl	>100	>100	ND	ND	ND	0
Bilirubin	mg/dl	0.5	Negative	ND	ND	ND	0
Serum biochemistry							
ALT	U/l	97	135	146	51	68	18–84
AST	U/l	90	122	142	20	19	16–53
ALKP	U/l	92	94	59	190	211	38–165
Urea	mg/dl	18.2	29.8	36.7	29.7	29.3	15.6–33.0
Creatinine	mg/dl	0.40	0.40	0.76	0.88	1.11	0.75–1.85
Albumin	g/dl	2.5	3.0	2.0	2.7	2.7	1.9–3.2
Total protein	g/dl	6.4	7.7	6.2	7.2	7.0	5.5–7.8
Total bilirubin	mg/dl	1.0	0.2	0.4	0.0	0.0	0–0.2
Total cholesterol	mg/dl	435	386	237	293	224	75–176
Triglyceride	mg/dl	>500	>2,500	56	716	781	7–77
Calcium	mg/dl	9.4	9.7	10.1	10.0	9.6	8.2–12.1
Phosphorus	mg/dl	2.7	3.2	1.4	3	3.6	2.6–6.0
Creatine kinase	U/l	1,045	95	3,575	582	216	89–312
Glucose	mg/dl	257	420	42	347	201	69–148
Amylase	U/l	ND	ND	2,352	2,152	1,799	501–2,684
Lipase	U/l	ND	ND	24	28	20	8–53
Serum amyloid A	µg/ml	ND	ND	13.7	0.5	0.2	0–6.5
GA	%	ND	ND	21.0	25.0	16.0	6.3–15.9

MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; $PvCO_2$, venous partial pressure of carbon dioxide; PvO_2, venous partial pressure of oxygen; AGAP, anion gap; BE, base excess; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GA, Glycoalbumin; ND, Not determined.

of anorexia, frequent vomiting, and further weight loss (body weight, 3.85 kg), the cat was readmitted on day 35. Diabetic ketoacidosis was diagnosed via blood tests and urinalysis (Table 1, day 35). We initiated infusion of regular insulin (0.04 IU/kg/hr) with physiological saline.

On day 38, infusion of regular insulin was increased to 0.2 IU/kg/hr, three bolus intravenous injections of regular insulin (0.13 IU/kg) were administered, and the cat resumed spontaneous feeding. However, diurnal hyperglycemia (268–306 mg/dl) persisted. At that point, we suspected the cat to have insulin resistance.

On day 39, subcutaneous administration of insulin detemir was initiated (0.67 IU/kg, q12hr) in addition to intravenous administration of regular insulin (0.1–0.2 IU/kg/hr) in an attempt to further decrease blood glucose concentration. For the same reason, regular insulin was increased to 0.3 IU/kg/hr on day 40 and insulin detemir was increased to 0.8 IU/kg (q12 hr) on day 41;

nonetheless, hyperglycemia persisted (daily glucose concentration was 302–438 mg/dl), indicating severe insulin resistance.

On day 42, there was a recurrence of urinary ketone bodies and metabolic acidosis, and blood glucose levels markedly dropped (11 mg/dl), leading to an adverse hypoglycemic event (loss of consciousness, convulsions). We discontinued regular insulin and initiated intravenous infusion of a 20% glucose solution.

On day 43, the cat was transferred to the Veterinary Medical Teaching Hospital of the Nippon Veterinary and Life Science University for investigation into the cause of the poor glycemic control and severe insulin resistance. At the time, the cat weighed 3.54 kg. Complete blood cell counts, serum biochemistry results, and venous blood-gas analysis were performed on day 43 (Table 1). Blood tests revealed anemia, hypoglycemia, hypophosphatemia, mild elevation of liver enzymes, mild azotemia, increased creatine kinase levels, hypernatremia, mild hyperkalemia, hyperchloremia, elevated serum amyloid A (SAA) levels, and elevated glycoalbumin (GA) levels [10]. Abdominal ultrasound examination revealed normal-sized adrenal glands (left, 3.3 mm; right, 4.6 mm). Thyroxine levels (1.46 µg/dl; reference interval: 0.5–4.0 µg/dl) and insulin-like growth factor-1 (IGF-1) levels (98 ng/ml; reference interval: mean=365.9, SD=192; n=15) were normal [16]. This led to the exclusion of concurrent hyperadrenocorticism, hyperthyroidism, and acromegaly.

We initiated administration of physiological saline, and when blood glucose increased to 132 mg/kg, we also initiated regular insulin administration (0.02 IU/kg/hr). Regular insulin was gradually increased (0.16–0.24 IU/kg/hr, daily insulin dose 3.84–5.76 IU/kg) with increasing blood glucose level and dietary feeding.

By day 44, we suspected AIA for exogenous insulin, such as regular insulin and insulin detemir, as the cause of severe insulin resistance. It has been reported that intravenous glargine and regular insulin have similar effects on blood glucose reduction [11, 17]. Therefore, we discontinued intravenous administration of regular insulin and initiated intravenous administration of insulin glargine (0.32–0.4 IU/kg/hr, daily dose 7.68–9.6 IU/kg). However, hyperglycemia persisted (408–444 mg/dl).

On day 45, we initiated prednisolone (1.5 mg/kg subcutaneously, q24 hr) to suppress the effects of suspected AIAs. In previous reports, cats with pemphigus foliaceus (an autoimmune disease) were treated with prednisolone at a median dosage of 2.2 mg/kg, q24 hr (range, 1.0–5.0 mg/kg, q24 hr) [2]. One cat treated with 1 mg/kg (q24 hr) prednisolone achieved remission after 2–3 months [2]. As such, we decided to administer prednisolone at 1.5 mg/kg (q24 hr), a relatively low dosage for the treatment of autoimmune diseases (the usual dosage is 2–4 mg/kg, q24 hr). Since the cat in this study had DM, we considered that a higher dosage (>2.0 mg/kg, q24 hr) might have had a hyperglycemic effect. High levels of human insulin antibody (>50 U/ml, reference range is <0.4 U/ml) were detected by FUJIFILM Monolith Co., Ltd. (Tokyo, Japan) using a radioimmunoassay (RIA). After the initial administration of prednisolone, the cat's appetite gradually increased, and insulin was adjusted according to blood glucose level and daily dietary intake.

On day 47, the blood glucose level stabilized (128–300 mg/kg); therefore, subcutaneous administration of insulin detemir (0.81 IU/kg, q12 hr) was initiated for reducing postprandial hyperglycemia, along with intravenous administration of insulin glargine (0.32–0.4 IU/kg/hr).

On day 50, as the cat's appetite fully recovered, intravenous administration of insulin glargine was discontinued, and subcutaneous injection of regular insulin (0.75 IU/kg) and insulin detemir (1.26 IU/kg) was initiated. The blood glucose level was maintained between 98 and 276 mg/dl.

From days 50 to 56, sufficient glycemic control could not be achieved (187–600 mg/dl on day 56) via subcutaneous injection of regular insulin (0.48–1.0 IU/kg) and insulin detemir (0.48–1.26 IU/kg). Therefore, subcutaneous administration of insulin detemir (0.5 IU/kg) and insulin degludec (0.25 IU/kg) was initiated on day 57. The insulin dose was gradually increased from days 57 to 61 (insulin detemir, 0.5–1.26 IU/kg; insulin degludec, 0.25–1.3 IU/kg). On days 60–61, acceptable glycemic control (86–403 mg/dl) was achieved. Body weight increased to 3.85 kg and the cat was discharged with a prescription of subcutaneous injection of insulin detemir (0.51 IU/kg, q12 hr), insulin degludec (1.0 IU/kg, q12 hr), and prednisolone (1 mg/kg, q24 hr). The owner was instructed to monitor glucose concentration.

On day 86, we performed complete blood counts and serum biochemistry (see Table 1). By day 86, body weight had increased to 4.6 kg and there was satisfactory glycemic control (GA=25%). Prednisolone treatment was altered to oral administration (0.6 mg/kg, q24 hr).

On day 232, continuously high human AIA levels (>50 U/ml) were reconfirmed by FUJIFILM Monolith Co., Ltd. using an RIA. On day 282, we performed complete blood counts and serum biochemistry (Table 1). Body weight had increased to 5.95 kg and satisfactory glycemic control was achieved (GA=16%) [10]. The medication being administered was prednisolone (0.13 mg/kg orally, q24 hr), insulin degludec (0.58 IU/kg subcutaneously, q12 hr), and insulin detemir (0.33 IU/kg subcutaneously, q12 hr).

Four serum samples, collected on different days (days 106, 169, 232, and 471) in the present case, were analyzed to determine levels of insulin-binding IgG in our laboratory using an enzyme-linked immunosorbent assay (ELISA). In addition, serum or plasma samples from healthy cats (n=29) and plasma samples from diabetic cats (n=10: 8 were on insulin therapy, 2 were not) were analyzed to determine levels of insulin-binding IgG. Samples were stored at −30°C until analysis. Insulin-binding IgG concentration was measured by modifying an existing ELISA protocol [18]. In short, a 96-well microplate (NUNC MaxiSorp, Thermo Fisher Scientific, Inc., Waltham, MA, USA) was coated with human insulin (Sigma-Aldrich, St. Louis, MO, USA) (4 µg/well), and serum or plasma samples, diluted 100 times, were added. Anti-feline IgG antibodies, labeled with horseradish peroxidase (Novus Biologicals, Littleton, CO, USA), were added as a secondary antibody. A tetramethylbenzidine solution (Nacalai Tesque Inc., Kyoto, Japan) was used for detection. After incubation, 1 N sulfuric acid was added and the absorbance at 450 nm was measured with a microplate reader (iMark, Bio-Rad Laboratories, Inc., Hercules, CA, USA). All samples were measured in duplicate. For validation of the assay, intra- and inter-assay variation was analyzed. Linearity was evaluated by serial dilution of serum or plasma samples. Assay specificity was evaluated by supplementing the reaction with human insulin.

The intra- and inter-assay coefficients of variation for insulin-binding IgG levels ranged from 4.0 to 8.2% and from 3.2 to 8.1%, respectively. Serial dilution of serum samples showed suitable linearity (r=0.9995; Supplementary Fig. 1). There was no difference in the absorbance of insulin-binding IgG between serum and plasma samples (Supplementary Fig. 1). Addition of human insulin (1–1 × 10^4 ng/ml) to the wells markedly suppressed absorbance (Supplementary Fig. 2).

There was no significant difference in blood insulin-binding IgG concentrations between diabetic (n=10) and healthy cats (n=29) (P=0.1875, Mann-Whitney U Test) (Fig. 1). All blood samples from the present case (from days 106, 169, 232, and 471) exhibited markedly higher insulin-binding IgG concentrations than those from healthy cats or cats with DM (Fig. 1).

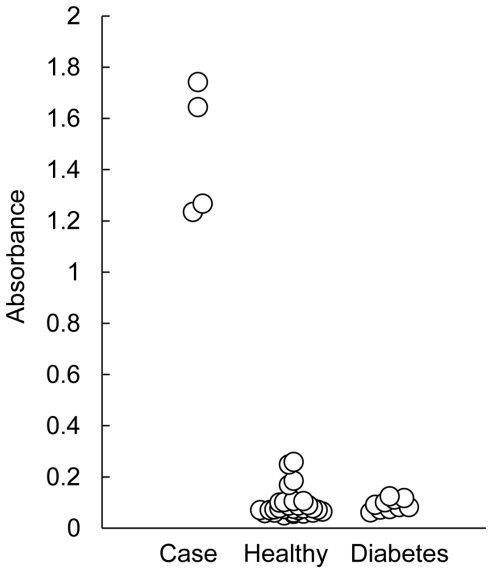

Fig. 1. Blood insulin-binding IgG in the present case (days 106, 169, 232, and 471), and in 29 healthy and 10 diabetic cats.

Informed consent (written) was obtained from all owners or legal custodians of the animals described in this work for the procedures undertaken.

In the current case, anti-human AIAs were detected. Furthermore, other concurrent diseases inducing severe insulin resistance were precluded. Therefore, in this case, severe insulin resistance might have been induced by AIAs against exogenous human insulin.

In a previous feline study, insulin antibodies were examined in treated (26 cats) and untreated diabetic cats (29 cats) [6]. Not all untreated diabetic cats had insulin antibodies, and four of the treated diabetic cats had insulin antibodies. One of the latter four cats required higher insulin doses than the others. As the cat from the cited study also had acromegaly and high IGF-1 levels, the high insulin requirement was likely caused by insulin antagonism of IGF-1. Thus, to our knowledge, insulin resistance due to AIAs in diabetic cats has never been observed.

An ELISA for anti-insulin IgG was previously developed for use in domestic cats [18]. In that study, all healthy cats possessed a small amount of plasma anti-insulin IgG. However, the physiological or pathological significance of anti-insulin IgG in cats remains unknown [12, 18]. AIAs are generated after administration of exogenous insulin preparations in people and dogs [3, 22]. Although these studies were not designed to test the relationship between AIA and glycemic control, no association was observed between AIA concentration and required insulin dose.

To date, there is no established treatment method for poor glycemic control due to AIAs in humans with diabetes. Various treatments have been administered in human patients, including changes in insulin preparations, steroid therapy, immunosuppression, oral hypoglycemic drugs, and plasma exchange [8, 9]. In the current feline case, treatment of initial diabetic ketoacidosis was successful. However, the cat had severe insulin resistance, which led to a second hospitalization for diabetic ketoacidosis. We suspected AIA production, and initiated treatment with prednisolone. This resulted in the gradual improvement of glycemic control and appetite.

One limitation of the present study was that the relationship between AIA production and insulin resistance could not be demonstrated. In fact, absorbance of insulin-binding IgG on days 106, 169, 232, and 471 in the present case were 1.267, 1.742, 1.235, and 1.644, respectively. As such, temporal reduction of insulin-binding IgG did not accompany the amelioration of clinical signs. In human study, severe insulin-resistant diabetic patients with AIA production have been reported [7, 19, 21]. In those studies, patients' ^{125}I-insulin-binding rates were measured to assess AIA production. After prednisolone treatment, the ^{125}I-insulin-binding rate decreased from 54% to 23% [7] and from 83.5% to <4% [19]. Meanwhile, non-insulin-resistant diabetic patients exhibited ^{125}I-insulin-binding rate <10% [21]. Furthermore, insulin antibody properties (affinity constant and binding capacity) did not change before and after prednisolone treatment [19]. In those three reports, insulin resistance was improved immediately after prednisolone treatment [7, 19, 21]. Although measurement of the ^{125}I-insulin-binding rate before and after prednisolone treatment is useful for determining AIA production in humans, such a system does not currently exist in veterinary medicine. As administration of prednisolone induced drastic amelioration of clinical signs and insulin resistance in this case, we suspect that AIA production was the cause of the observed severe insulin resistance. However, the potential relationship between AIA production and clinical insulin resistance in cats warrants further study. In addition, one possible explanation for insulin resistance in cats is inflammatory disease. However, in the present case, on day 43, SAA was 13.7 µg/ml, which is only slightly higher than the reference range (0–6.5 µg/ml). Previously, it was reported that cats with upper respiratory tract infections, pneumonia, pyometra, feline infectious peritonitis, trauma, and/or sepsis exhibited a median SAA of >100 µg/ml [20, 24]. In cats with diabetic ketoacidosis (n=8), the median SAA was reported as 4.1 µg/ml (interquartile range, 0.3–60.5 µg/ml) [24]. As such, the low level of inflammation (13.7 µg/ml) in the current case would not have induced insulin resistance to the extent that 1.5 IU/kg insulin would be needed twice a day. Furthermore, other concurrent diseases such as acromegaly and/or hyperadrenocorticism were precluded.

In conclusion, in the current case, AIAs were detected in a diabetic cat with severe insulin resistance. Serum insulin-binding IgG levels were markedly higher than the levels in healthy cats and other diabetic cats. Therefore, when diagnosing diabetic cats with severe insulin resistance, AIAs should be considered.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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