CASE REPORT

Serious diabetic ketoacidosis induced by insulin allergy and anti-insulin antibody in an individual with type 2 diabetes mellitus

Kaio Takahashi[1], Takatoshi Anno[1]*, Haruka Takenouchi[1], Hideyuki Iwamoto[1], Megumi Horiya[1], Yukiko Kimura[1], Fumiko Kawasaki[1], Kohei Kaku[1], Koichi Tomoda[1], Hideaki Kaneto[2]

[1]Department of General Internal Medicine 1, Kawasaki Medical School, Okayama, Japan, and [2]Department of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, Kurashiki, Japan

ABSTRACT

Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes mellitus, and is characterized by hyperglycemia, metabolic acidosis and increased total ketone body concentrations. The main mechanism of DKA is a lack of insulin in the body. It has been reported that some immunological response is associated with insulin therapy. Herein, we report a case of serious DKA, which was induced by insulin allergy and anti-insulin antibody. This case clearly shows that DKA can be induced by insulin allergy and anti-insulin antibodies in individuals with type 2 diabetes treated with insulin. Furthermore, we should know that as the required insulin dose might be very high under severe insulin resistance and serious DKA in such cases, we should increase the insulin dose appropriately while monitoring pH, base excess and other factors.

INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes mellitus, and is characterized by hyperglycemia, metabolic acidosis and increased total ketone body concentrations[1]. As the main mechanism of DKA is a lack of insulin in the body, DKA is often observed among patients with type 1 diabetes mellitus .

It has been reported that some immunological response is associated with insulin therapy[2]. Insulin allergy is still sometimes observed in clinical practice[3]. In addition, it is possible that patients with insulin allergy show positive for immunoglobulin G-derived insulin antibodies[4]. In general, anti-insulin antibodies are mainly induced in diabetes mellitus patients treated with insulin preparations. Both insulin allergy and anti-insulin antibodies can cause instability in glycemic control.

CASE REPORT

A 56-year-old Japanese woman was brought to the emergency room with coma. She was diagnosed as type 2 diabetes mellitus at the age of 47 years, and was taking antidiabetic drugs. Her

history included spinal disc herniation at age 54 years, and she was treated with insulin preparations (insulin human and aspart). After then, she started taking antidiabetic drugs, but she was treated again with insulin degludec at age 55 years for half a year. After her interruption of therapy for 7 months, she re-started receiving insulin therapy. One week after starting insulin glargine, however, local redness was gradually observed at the injection site. Therefore, glargine was changed to degludec/aspart. One week after changing insulin preparation, local redness at the injection site was still observed. As shown in Table 1, as she had hyperglycemia, metabolic acidosis and increased total ketone body concentrations, we finally diagnosed her as DKA. Two weeks after re-starting insulin, DKA was induced together with general fatigue.

On admission, we started to treat her hyperglycemic crises with continuous insulin infusion using human insulin. We gradually increased the continuous insulin dose, and DKA was improved with 18 units/h of insulin infusion. As the result, a total insulin dose for 24 h reached >300 units (Figure 1a). We decreased continuous insulin dose, but her blood glucose level increased again, together with metabolic acidosis. Therefore, we maintained the insulin infusion dose to treat metabolic acidosis and investigated the cause of insulin resistance.

Table 1 | Laboratory data observed in the emergency room

Variable	Result	Reference range
Peripheral blood		
White blood cells (/μL)	21,880	3,300–8,600
Neutrophil (%)	82.0	52.0–80.0
Eosinophil (%)	1.0	1.0–5.0
Red blood cells ($\times 10^4$/μL)	491	386–492
Hemoglobin (g/dL)	15.6	11.6–14.8
Hematocrit (%)	48.7	35.1–44.4
Platelets ($\times 10^4$/μL)	37.1	15.8–34.8
Blood biochemistry		
Total protein (g/dL)	7.8	6.6–8.1
Albumin (g/dL)	4.9	4.1–5.1
Total bilirubin (mg/dL)	0.5	0.4–1.5
AST (U/L)	64	13–30
ALT (U/L)	45	7–23
LDH (U/L)	304	124–222
ALP (U/L)	415	106–322
γ-GTP (U/L)	30	9–32
BUN (mg/dL)	32	8–20
Creatinine (mg/dL)	0.81	0.46–0.79
Uric acid (mg/dL)	13.1	2.6–5.5
Creatine Kinase (U/L)	40	41–153
Amylase (U/L)	30	44–132
P-Amylase (IU/L)	17	19–53
Sodium (mmol/L)	134	138–145
Potassium (mmol/L)	5.3	3.6–4.8
Chloride (mmol/L)	93	101–108
Infectious marker		
CRP (mg/dL)	7.2	<0.14
Procalcitonin (ng/mL)	6.67	0.00–0.05
Endocrinology marker		
ACTH (pg/mL)	30.8	7.2–63.3
Cortisol (μg/dL)	12.5	6.24–18.0
Diabetes marker		
Plasma glucose (mg/dL)	520	
Hemoglobin A1c (%)	11.9	4.9–6.0
Glycoalbumin (%)	31.7	12.4–16.3
Total ketone body (μmol/L)	17,304.0	0.0–130.0
Acetoacetate (μmol/L)	3,698.0	0.0–55.0
β-Hydroxybuterate (μmol/L)	13,606.0	0.0–85.0
Anti-GADAb (U/mL)	<5.0	<5.0
Anti-IA-2Ab (U/mL)	<0.6	0–0.3
Anti-ICAAb (JDF UNIT)	Negative	<1.25
Anti-ZnT8Ab (U/mL)	<10.0	<15.0
Thyroid marker		
TSH (μU/mL)	1.550	0.400–6.000
Free triiodothyronine (pg/mL)	3.17	2.5–4.20

Table 1. (Continued)

Variable	Result	Reference range
Free thyroxine (ng/dL)	1.17	0.80–1.60
TRAb (IU/L)	<0.8	<1.0
Anti-TPOAb (IU/mL)	<9.0	<16.0
Anti-TgAb (IU/mL)	<10.0	<28.0
Blood gas analysis		
pH	6.932	7.360–7.460
PCO_2 (mmHg)	18.5	34.0–46.0
PO_2 (mmHg)	73.6	80.0–90.0
$HCO3^-$ (mEq/L)	3.7	24.0–32.0
BE (mEq/L)	−30.4	−2.5 − 2.5
Lactate (mEq/L)	2.30	0.63–2.44
Urinary test		
Urinary pH	5.0	5.0–7.5
Urinary protein	1+	−
Urinary sugar	3+	−
Urinary ketone body	3+	−
Urinary bilirubin	−	−
Urinary blood	−	−

γ-GTP, γ-glutamyltranspeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-GAD antibody, anti-glutamic acid decarboxylase antibody; Anti-IA-2Ab, anti-insulinoma-associated protein-2 antibody; Anti-ICAAb, anti-islet cell antibody; Anti-TgAb, anti-thyroglobulin Ab; Anti-TPOAb, anti-thyroid peroxidase Ab; Anti-ZnT8Ab, anti-zinc transporter8Antibody; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; P-Amylase, pancreatic amylase; TRAb, anti-thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.

Endocrine hormone levels were within the normal range. The patient's islet-specific autoantibodies were all negative. However, anti-insulin antibody was positive (>5,000 nU/mL), and its binding rate was as high as 84.2%. Her plasma insulin level was elevated to 136.4 μU/mL, and her C-peptide level was 1.4 ng/mL 4 days after admission. The patient's non-specific immunoglobulin E level was elevated to 396 IU/mL. Above all, her specific immunoglobulin E level to human insulin was class IV on radioallergosorbent test. Scatchard analysis plots of insulin autoantibodies showed that its binding rate of anti-insulin antibody was very high (Figure 1b). Based on such findings, we diagnosed her as serious DKA induced by insulin allergy and anti-insulin antibody. After improvement of DKA, we stopped insulin therapy and treated her with 500 mg of metformin and 0.6 mg of voglibose.

Figure 1 | (a) Time course of clinical parameters and continuous insulin infusion rate in the present patient. On admission to a high care unit, we started to treat her hyperglycemic crises. Although we started continuous insulin infusion, her hyperglycemic condition and metabolic acidosis were not improved. After increasing dose of continuous insulin up to 18 units/h, hyperglycemia and metabolic acidosis were finally improved. As a result, the total insulin dose for 24 h reached >300 units. We gradually tapered the continuous insulin dose at once, but her glucose level increased again together with metabolic acidosis. (b) A Scatchard analysis of insulin antibody under the diabetic ketoacidosis condition. K1 and K2 show affinity constant at the high- and low-affinity site, respectively. B1 and B2 show binding capacity at the high- and low-affinity site, respectively.

(a)

High Care Unit (HCU)

(b)

Scatchard Plot

$K1=1.41\times10^{-2}$ $(1/10^{-8}M)$
$K2=4.83\times10^{-3}$ $(1/10^{-8}M)$
$B1=188$ $(10^{-8}M)$
$B2=1040$ $(10^{-8}M)$
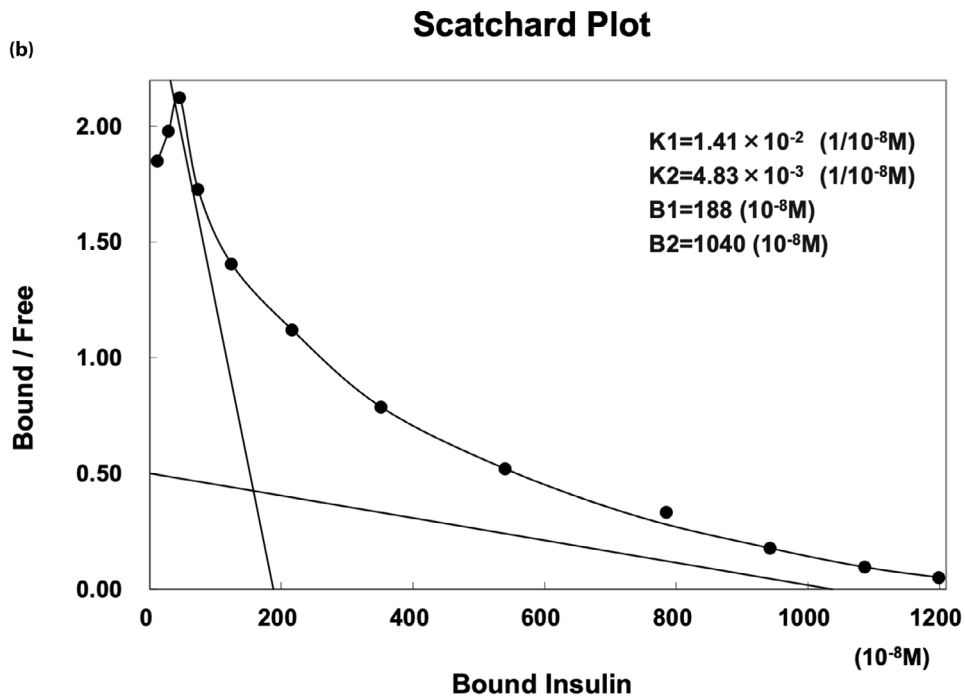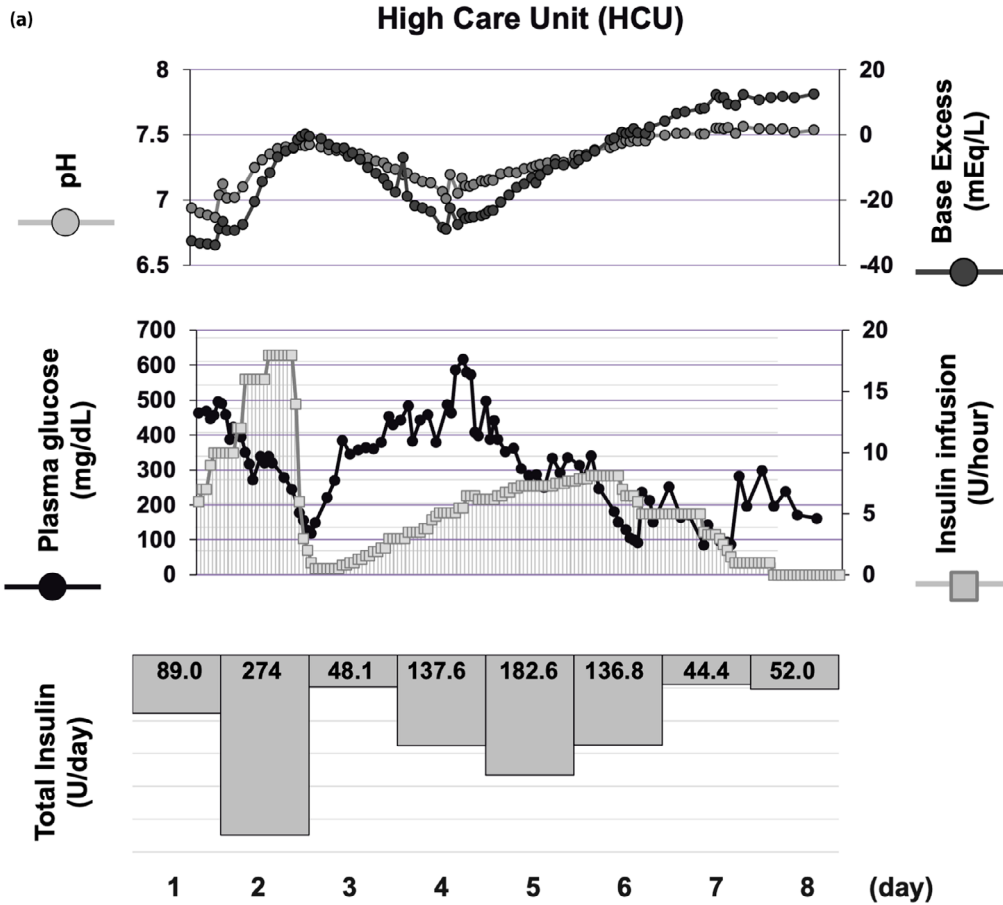
DISCUSSION

In the present report, we show serious DKA in an individual with type 2 diabetes. Interestingly, as DKA was induced by severe insulin resistance complicated with insulin allergy and anti-insulin antibodies, she required very high-dose insulin for improvement of DKA. DKA is often observed among patients with type 1 diabetes, but it might be induced in patients with type 2 diabetes in special situations[5]. In addition, if insulin antibodies are detected in patients with no history of insulin administration, insulin autoimmune syndrome is suspected[6]. It was reported that the characteristics of the anti-insulin antibodies of insulin autoimmune syndrome showed an extremely low affinity constant and a high binding capacity. In general, anti-insulin antibodies, which are produced by insulin therapy, rarely have a significant effect on glycemic control, but it is possible that anti-insulin antibodies after insulin therapy have similar properties to antibodies in insulin autoimmune syndrome, leading to severe blood glucose fluctuation[7].

As insulin allergy and anti-insulin antibody could not be detected immediately, we had no choice but to carry out therapy for DKA without noticing the presence of them. There have been several reports about individuals with severe insulin resistance mediated by anti-insulin antibody[8–10]. However, such individuals did not suffer from DKA. In addition, the present case suggests that once we use exogenous human insulin and/or human insulin-analog, multiple classes of antibodies against insulin, such as immunoglobulin E and immunoglobulin G antibodies, can be induced simultaneously, resulting in severe insulin resistance. Furthermore, we believe that as the patient had severe insulin resistance due to anti-insulin antibody, she suffered from DKA and required a very high dose of insulin to improve DKA. In such a case, we had no choice but to increase the insulin dose against metabolic acidosis to save her life.

Treatments for diabetes mellitus patients with insulin allergy and anti-insulin antibodies have not been established yet, and various treatments have been tried[11]. It was reported that metformin combined with an α-glucosidase inhibitor showed favorable effect on anti-insulin antibodies[12]. Laboratory data for the present patient before re-starting insulin were as follows: plasma glucose 275 mg/dL, glycated hemoglobin 11.8%, plasma insulin 7.0 μU/mL and C-peptide level 2.2 ng/mL, although we did not check her anti-insulin antibody at that time. These results showed that her endogenous insulin functioned appropriately, even without any insulin preparation. Therefore, we treated her with metformin and α-glucosidase inhibitor, but she experienced hypoglycemia together with hyperinsulinemia. Therefore, it seems that insulin secretory capacity was preserved after improvement of DKA, although hypoglycemia and hyperinsulinemia were observed due to the possible remaining antibodies. These data also suggest that the patient's anti-insulin antibody binds to not only exogenous insulin, but also endogenous insulin. We considered she was well treated with glucocorticoids therapy, which is one of the treatments for anti-insulin antibodies, because her local redness disappeared. Also, as we though that the therapy with metformin and α-glucosidase inhibitor therapy was effective for her, we continued these anti-diabetic drugs. Considering these points, the patient's endogenous insulin was, at least in part, improved, although her glycemic control was not improved enough.

Taken together, we should bear in mind that if insulin is used at present or previously, DKA can be induced by insulin allergy and anti-insulin antibodies.

DISCLOSURE

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