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【 CASE REPORT 】

Glutamic Acid Decarboxylase Autoantibody-negative Slowly Progressive Type 1 Diabetes Mellitus: A Case Report and Literature Review

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Abstract:
A 59-year-old non-obese Japanese woman developed diabetes mellitus with a negative glutamic acid decarboxylase autoantibody (GADA) test result. Her hyperglycemia was initially well controlled by oral hypoglycemic agents; however, despite continued treatment the hyperglycemia gradually worsened. As she had endogenous insulin deficiency and tested positive for insulin autoantibody (IAA), insulin therapy was initiated. Few studies have investigated GADA-negative patients with slowly progressive type 1 diabetes mellitus (SPT1D). Our IAA-positive SPT1D patient progressed from the clinical onset of diabetes mellitus to starting insulin therapy relatively quickly (1.5 years), similarly to other previously reported non-obese patients with GADA-positive SPT1D.

Key words: C-peptide immunoreactivity, human leukocyte antigen, insulin autoantibody, type 1 diabetes mellitus

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Introduction

Type 1 diabetes mellitus (T1D) is a heterogeneous, metabolic disease characterized by an immune-mediated progressive destruction of pancreatic beta cells, usually leading to an absolute insulin deficiency (1). The rate of beta cell destruction is quite variable from case to case, being rapid in some individuals (mainly children) and slow in others (mainly adults); the former condition is referred to simply as T1D, while the latter is referred to as latent autoimmune diabetes in adults (LADA) (2).

There are some ethnic heterogeneities in the clinical presentation and genetic background of T1D (3-5). In Japan, T1D is classified into three subtypes according to the manner of onset and progression: fulminant, acute-onset, and slowly progressive (6). Slowly progressive T1D (SPT1D) which is related to LADA in other countries, including Western and Asian populations, is characterized by a gradual decrease in endogenous insulin secretion, clinical features similar to those of type 2 diabetes mellitus (T2D), and the presence of circulating autoantibodies against islet antigens (7). Patients with SPT1D eventually become dependent on insulin therapy, whereas patients with LADA require insulin therapy less frequently (8, 9).

Islet-related autoantibodies reflect the autoimmune destruction of pancreatic beta cells in patients with T1D (10). The major autoantibodies in clinical use include glutamic acid decarboxylase autoantibodies (GADA), islet cell antibodies (ICA), insulinoma-associated antigen-2 autoantibodies (IA-2Ab), insulin autoantibodies (IAA), and zinc transporter 8 autoantibodies (ZnT8Ab).

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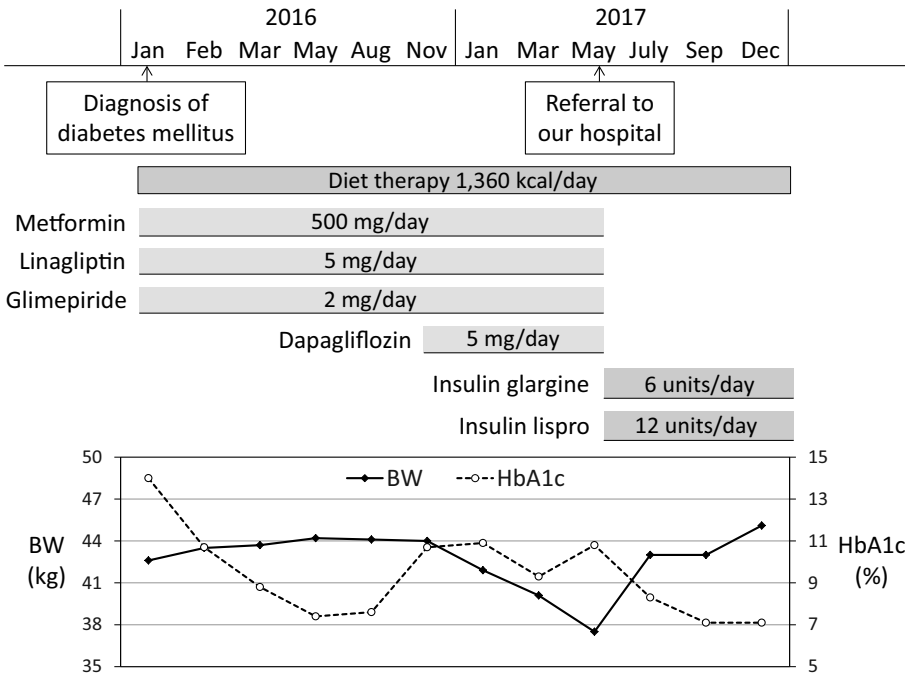

Figure. **Clinical course. The patient had not received insulin therapy before May 2017, when she was diagnosed with slowly progressive type 1 diabetes mellitus associated with decreased endogenous insulin secretion, tested positive for insulin autoantibodies, and started insulin therapy. BW: body weight, HbA1c: glycated hemoglobin**

Almost all reported cases of LADA or SPT1D have been GADA-positive patients, and studies on GADA-positive LADA or SPT1D have suggested some differences in the clinical features between patients with low and high titers of GADA (2, 11, 12). For example, patients with higher GADA titers may have a higher rate of decline in endogenous insulin secretion, more difficulty controlling hyperglycemia, and a higher frequency of positivity for other islet-related autoantibodies or of autoimmunity in other organs. However, little is known about GADA-negative LADA or SPT1D. Recent studies of Western or Asian patients with LADA have suggested the utility of testing for IA-2Ab, ZnT8Ab, or IAA for diagnosing LADA in GADA-negative patients with phenotypic T2D (13-17). In Japan, only a few case reports are available on GADA-negative patients with SPT1D who tested positive for IA-2Ab or ZnT8Ab (18, 19).

We herein report the case of a GADA-negative but IAA-positive Japanese patient with SPT1D and review previously reported cases of GADA-negative SPT1D.

Case Report

A 61-year-old Japanese woman was admitted to our hospital in May 2017 because of severe hyperglycemia. Her medical and family history were unremarkable. She had never smoked and did not drink alcohol. She had never been obese, her body weight (BW) was 44 kg when she was 20 years of age, and she reached a maximum BW of 50 kg at 58 years of age. The patient developed thirst, polyuria, and fatigue in November 2015 (at 59 years of age) and visited a local doctor in January 2016 because of persistent thirst, polyuria, and fatigue, and a BW loss (5 kg) over the 2-month period. Her BW, blood pressure, and pulse rate were 42.6 kg, 117/72 mmHg, and 93 beats per minute, respectively, and blood testing showed high levels of casual plasma glucose (530 mg/dL) and glycated hemoglobin (HbA 1c) (14.0%), and normal levels of serum total cholesterol (199 mg/dL) and triglycerides (99 mg/dL); she tested negative for GADA (<5.0 U/mL) (Cosmic, Tokyo, Japan). The patient was diagnosed with diabetes mellitus and received medical treatment with diet therapy (1,360 kcal/day) and oral hypoglycemic agents, including metformin, linagliptin, and glimepiride (Figure). She experienced an improvement in her hyperglycemia and symptoms, and her HbA1c values decreased to approximately 7% within 6 months. However, the hyperglycemia gradually became poorly controlled, despite continuing the same treatment, and she experienced recurrent hyperglycemic symptoms of thirst, polyuria, fatigue, and BW loss. The patient was referred to our hospital and was admitted in May 2017.

Upon admission, the patient's height and BW were 149 cm and 37.5 kg, respectively [body mass index (BMI): 16.9 kg/m^2]. Her body temperature, blood pressure, and pulse rate were 36.6℃, 104/71 mmHg, and 65 beats per minute. Funduscopy detected no diabetic retinopathy. No thyroid struma, chest rales, heart murmurs, abdominal tenderness, or peripheral edema were present. The patient had no numbness in her hands or feet and had normal Achilles tendon reflexes. A blood analysis revealed high levels of casual plasma glucose (350 mg/dL) and HbA1c (10.8%), and a urinalysis was

Table 1. Laboratory Findings at the Time of Admission (May 2017).

Hematology			
Red blood cells	399×10⁴	/μL	(386–492)
Hemoglobin	12.2	g/dL	(11.6–14.8)
Hematocrit	36.5	%	(35.1–44.4)
White blood cells	5,400	/μL	(3,300–8,600)
Platelets	22.6×10⁴	/μL	(15.8–34.8)
Blood chemistry			
Casual plasma glucose	355	mg/dL	(70–139)
Glycated hemoglobin (HbA1c)	10.8	%	(4.6–6.2)
Total protein	6.9	g/dL	(6.6–8.1)
Albumin	4.2	g/dL	(4.1–5.1)
Total cholesterol	219	mg/dL	(142–248)
Triglycerides	68	mg/dL	(30–117)
Aspartate aminotransferase	18	IU/L	(13–30)
Alanine aminotransferase	19	IU/L	(7–23)
Creatine kinase	44	IU/L	(41–153)
Urea nitrogen	26.0	mg/dL	(8.0–18.4)
Creatinine	0.77	mg/dL	(0.46–0.79)
Uric acid	5.2	mg/dL	(2.6–5.5)
Sodium	138	mEq/L	(138–145)
Potassium	4.2	mEq/L	(3.6–4.8)
Chloride	100	mEq/L	(101–108)
C-reactive protein	0.02	mg/dL	(<0.15)
Thyroid-stimulating hormone	1.00	μIU/mL	(0.5–5.0)
Free thyroxine	1.05	ng/dL	(0.9–1.7)
Glutamic acid decarboxylase autoantibody	< 5.0	U/mL	(<5.0)
Islet cell antibody	Negative		
Insulinoma-associated antigen-2 autoantibody	< 0.4	U/mL	(<0.4)
Insulin autoantibody	185.9	nU/mL	(<125.0)
Zinc transporter 8 autoantibody	< 15.0	U/mL	(<15.0)
Urinalysis			
Specific gravity	1.032		(1.005–1.020)
Glucose	Positive		
Ketone bodies	Negative		
Protein	Negative		
Occult blood	Negative		

The reference range for each parameter is shown in parentheses.

The blood and urine samples were taken at 10 AM in a postprandial state. The patient had never received insulin therapy.

negative for ketone bodies (Table 1). The patient tested negative for GADA (<5.0 IU/mL), ICA (a negative qualitative test result), IA-2Ab (<0.4 U/mL), and ZnT8Ab (<15.0 U/mL), but an IAA test (185.9 nU/mL; reference range, <125.0 nU/mL) (Yamasa, Tokyo, Japan) was positive. Abdominal computed tomography detected no abnormalities in the liver, spleen, pancreas, or kidneys.

To resolve the hyperglycemia, the patient started multiple daily injections using basal once-daily glargine and mealtime lispro on the day of admission (Figure).

A meal load test performed on day 3 of admission revealed a low serum C-peptide immunoreactivity (S-CPR) level of 1.0 ng/mL after eating breakfast (Table 2A), suggesting T1D with a decreased endogenous insulin secretion capacity. Human leukocyte antigen (HLA) typing revealed the presence of A*24:02/26:03, B*15:01/40:02, and C*03:03/03:04 class I genes and DRB1*09:01/(-), DQB1*03:03/(-), DQA1*03:02/(-), and DPB1*02:01/05:01 class II genes. The patient tested negative for anti-nuclear antibodies, rheumatoid factor, pituitary gland autoantibodies, thyroid peroxidase autoantibodies, thyroglobulin autoantibodies, thyroid-stimulating hormone receptor autoantibodies, gastric parietal cell autoantibodies, intrinsic factor autoantibodies, and adrenal cortex autoantibodies.

The patient was discharged on day 10 of admission after a self-management diabetes education program.

She continued diabetes treatment with multiple daily injections (insulin glargine 6 units/day and insulin lispro 12 units/day) at the outpatient clinic of our hospital. In December 2017, her BW was 45.1 kg, and laboratory findings showed an HbA1c value of 7.1% (Figure). A glucagon stimulation test revealed S-CPR levels of 0.3 ng/dL (Ta-

Table 2. Evaluation of Residual Endogenous Insulin Secretory Capacity.

A. Meal load test (May 2017)		
	Before	2 h
S-CPR (ng/mL)	0.2	1.0
Plasma glucose (mg/dL)	80	306

Blood samples were taken on day 3 after admission before and 2 h after ingestion of a 450 kcal breakfast (9 AM).
The patient had started multiple daily injections with insulin glargine (at bedtime) and insulin lispro (at each mealtime) on the day of admission. The injection of insulin lispro was briefly discontinued at breakfast on the day of the test.
S-CPR: serum C-peptide immunoreactivity

B. Glucagon stimulation test (December 2017)		
	Before	6 min
S-CPR (ng/mL)	0.2	0.3

Blood samples were taken in a fasting state before and 6 min after glucagon (1 mg) was administered intravenously (9 AM).

ble 2B), indicating that she was in an insulin-dependent state. She tested negative for GADA (<5.0 IU/mL), ICA (a negative qualitative test result), IA-2Ab (<0.4 U/mL), and ZnT8Ab (<15.0 U/mL), and positive for IAA (565.5 nU/mL). The patient's course has been uneventful and there have been no complications during insulin therapy.

Discussion

The patient, a Japanese woman with hyperglycemic symptoms that had persisted for 2 months, was diagnosed with diabetes mellitus with a negative GADA test result and started medical treatment with appropriate diet therapy and oral hypoglycemic agents, which effectively controlled her hyperglycemia within 6 months (Figure). However, her hyperglycemia gradually deteriorated despite the continuation of diabetes treatment. She had endogenous insulin deficiency, as assessed by low S-CPR levels (Table 2A), and tested positive for IAA. She started insulin therapy 18 months (1.5 years) after the clinical onset of diabetes mellitus.

Patients with the acute-onset subtype of T1D may have a period, often shortly after the initiation of insulin therapy, when they experience a reduction in their exogenous insulin requirement despite, maintaining good metabolic control. This phenomenon is referred to as the remission or "honeymoon phase" of T1D and may last for months or years (20). The presumed pathogenic mechanisms underlying the "honeymoon phase" include beta cell rest, reversal of glucotoxicity, and the alleviation of islet autoimmune processes through adequate control of hyperglycemia with exogenous insulin therapy (21). On the other hand, patients with SPT1D may experience a period (months or years) in which their glycemic control can be improved with an appropriate diet and oral hypoglycemic agents, before they require insulin therapy (7). In the present case (Figure and Table 2), the clinical course of our patient before and after the initiation of exogenous insulin therapy was not explained by the "honeymoon phase" of acute-onset T1D but was consistent with that typical of SPT1D.

Table 3 presents a summary of reported Japanese patients with SPT1D who tested negative for GADA. The cases include adults of both sexes and different ages. The time from the onset of diabetes mellitus to the initiation of insulin therapy varied among the cases, ranging from 1-4 years. The patients had the HLA class II DRB1*04:05-DQB1*04:01 or DRB1*09:01-DQB1*03:03 haplotype. They tested positive for one or more islet-related autoantibodies other than GADA, such as IA-2Ab, ZnT8Ab, and IAA. Our patient is the first reported case of GADA-negative SPT1D associated with IAA positivity.

IAA is a circulating autoantibody against insulin, specific to beta-cell autoantigens, which is frequently detected in patients with new-onset T1D (10, 23). Only a small portion of GADA-positive LADA patients test positive for IAA (17, 24), whereas a study of Japanese patients revealed IAA positivity in approximately one-third of GADA-positive patients with SPT1D before the initiation of insulin therapy (12). IAA can also be detected in patients with insulin autoimmune syndrome, a rare metabolic disorder that is characterized by severe spontaneous hypoglycemic attack (25). However, exogenous insulin injection can elicit antibody responses that cannot be distinguished from IAA production (10). In the present case, the patient tested positive for IAA before she started insulin therapy, during the course of decreasing endogenous insulin secretion accompanied by severe chronic hyperglycemia. These findings indicate that the IAA positivity in our patient sensitively reflected the autoimmune destruction of pancreatic beta cells and helped us to make the diagnosis of SPT1D.

Studies of GADA-positive LADA have revealed that the endogenous insulin secretion in non-obese patients tends to decrease more quickly than that in obese patients (9). A study of GADA-positive Japanese patients with SPT1D also revealed that non-obese patients are likely to exhibit greater decreases in endogenous insulin secretion in comparison to obese patients; they are also likely to have a shorter period between the onset of diabetes mellitus and the initiation of insulin therapy, with a median period of approximately 1.5 years (26). On the other hand, patients with LADA or SPT1D who have a lower GADA titer or a smaller number of other islet-related autoantibodies may have a slower decline in endogenous insulin secretion (9, 11, 12, 27), whereas the presence of IAA is a predictor of a rapid decrease in endogenous insulin secretion (15). In the present case, our non-obese GADA-negative patient with single IAA positivity exhibited a short duration from the onset of diabetes mellitus to the initiation of insulin therapy, which was similar to the course of previously reported non-obese Japanese patients with GADA-positive SPT1D (26), and she ex-

Table 3. Summary of Reported Japanese Patients with Slowly Progressive Type 1 Diabetes Mellitus Who Tested Negative for Glutamic Acid Decarboxylase Autoantibodies.

Ref.	Sex	Age at diabetes onset (years)[a]	HLA-DRB1	HLA-DQB1	History of obesity	History of hypertension	History of dyslipidemia	Family history of diabetes	Time from diabetes onset to starting insulin therapy (years)	BMI at the time of starting insulin therapy (kg/m^2)	HbA1c at the time of starting insulin therapy (%)	Diabetic retinopathy	Islet-related autoantibodies detected	Thyroid autoantibodies detected[b]	Other findings
(18)	Male	32	04:05/ 13:02	04:01/ 06:04	[+]	[–]	[–]	[+][c]	4	21.5	8.7[d]	None	IA-2Ab	N/D	Positivity for PA-IgG
(19)	Male	89	04:05/ 11:01	04:01/ 03:01	[+]	[–]	[–]	[–]	1	22.2	11.0	None	IA-2Ab and ZnT8Ab	None	History of polymyalgia rheumatica
Present case	Female	59	09:01/ (–)	03:03/ (–)	[–]	[–]	[–]	[–]	1.5	16.9	10.8	None	IAA	None	None

[a]Diabetes onset is when the patient was diagnosed with diabetes mellitus or developed hyperglycemia symptoms, including thirst, polyuria, and body weight loss.
[b]Thyroid autoantibodies include thyroid peroxidase autoantibody, thyroglobulin autoantibody, or thyroid-stimulating hormone receptor autoantibody.
[c]The patient's maternal grandmother and aunt had diabetes mellitus.
[d]HbA1c (%) was estimated to be the National Glycohemoglobin Standardization Program-equivalent value (%), calculated using the formula HbA1c (%)=HbA1c (Japan Diabetes Society, JDS) (%)+0.4% (22).
BMI: body mass index, HbA1c: glycated hemoglobin, HLA: human leukocyte antigen, IA-2Ab: insulinoma-associated antigen-2 antibody, IAA: insulin autoantibody, N/D: not described, PA-IgG: platelet-associated immunoglobulin G, ZnT8Ab: zinc transporter 8 antibody

perienced progression to almost complete insulin deficiency within 2 years after the onset of diabetes mellitus (Table 2B).

T1D is a multifactorial disease caused by a complex interaction of genetic and environmental factors. Among candidate genes, HLA class II confers the greatest risk of T1D, but alleles associated with T1D differ among ethnic groups due to differences in allele distribution in the general population (28, 29). It is thought that LADA shares susceptible class II HLA genes with T1D in Caucasian populations (30), whereas studies of other ethnic groups, including Chinese populations, have suggested that the susceptibility genes of T1D and LADA are distinct (31, 32). In Japan, the HLA associations with SPT1D differ from those with fulminant T1D, whereas the HLA associations with SPT1D are similar to those with acute-onset T1D (albeit weaker) (33, 34). The susceptible HLA class II genes in Japanese patients with SPT1D include HLA DRB1*04:05-DQB1*04:01 and DRB1 *09:01-DQB1*03:03 haplotypes, which are associated with insulin deficiency (35). In our patient, the presence of the HLA DRB1*09:01-DQB1*03:03 haplotype likely contributed to the development of SPT1D.

The clinical characteristics of typical GADA-positive LADA or SPT1D (2, 7) include those of T2D, such as obesity, dyslipidemia, hypertension, fatty liver, or a family history of diabetes mellitus. GADA-positive patients with LADA or SPT1D also often have other organ-specific autoimmune disorders, such as autoimmune thyroid diseases (11, 12). The previously reported GADA-negative Japanese patients with SPT1D (Table 3) had a history of obesity, a family history of diabetes mellitus, and organ-specific autoantibodies, such as platelet-associated immunoglobulin G. In the present case, our patient did not have obesity, hypertension, dyslipidemia, fatty liver, or a family history of diabetes mellitus, and a series of serum autoantibody tests did not detect any organ-specific autoimmune disorders other than IAA-positive SPT1D.

In conclusion, we reported the case of a GADA-negative non-obese Japanese patient with IAA-positive SPT1D who experienced a relatively rapid progression (1.5 years) from the clinical onset of diabetes mellitus to requiring insulin therapy, similarly to previously reported non-obese cases of GADA-positive SPT1D. A combination of serial changes in S-CPR levels, tests for islet-related autoantibodies other than GADA, and an HLA gene analysis was useful for making the diagnosis of SPT1D in the present case. Whether the clinical features vary between GADA-negative and GADA-positive patients with SPT1D remains unclear. Similar cases should be accumulated to clarify the characteristics of GADA-negative T1D associated with the slowly progressive autoimmune destruction of pancreatic beta cells.

The authors state that they have no Conflict of Interest (COI).

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