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CASE REPORT

Case of slowly progressive type 1 diabetes mellitus with drastically reduced insulin secretory capacity after immune checkpoint inhibitor treatment for advanced renal cell carcinoma

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Abstract

We encountered a 55-year-old Japanese man with advanced renal cell carcinoma and slowly progressive type 1 diabetes mellitus (SPT1DM), whose insulin secretory capacity was drastically reduced for a brief period after only one cycle of immune checkpoint inhibitor (ICI) treatment. The patient had been diagnosed with type 2 diabetes at the age of 53 years and was treated using oral hypoglycemic agents. However, 2 years later, he was diagnosed with SPT1DM and autoimmune thyroiditis, based on the presence of anti-glutamic acid decarboxylase antibodies (GADA) and thyroid autoantibodies, which was accompanied by advanced renal cell carcinoma. At that time, his insulin secretory capacity was preserved (CPR 2.36 ng/mL), and good glycemic control was maintained using only medical nutrition therapy (HbA1c 6.3%). He subsequently developed destructive thyroiditis approximately 2 weeks after the first cycle of ICI treatment using nivolumab (a programmed cell death-1 inhibitor) and ipilimumab (a cytotoxic T-lymphocyte-associated antigen-4 inhibitor) for advanced renal cell carcinoma. Three weeks later, his plasma glucose level markedly increased, and we detected absolute insulin deficiency and hypothyroidism. Human leukocyte antigen (HLA) analysis revealed haplotypes indicating susceptibility to type 1 diabetes mellitus (T1DM) or autoimmune thyroiditis (HLA genotype, DRB1-DQB1 *09:01–*03:03/*08:03–*06:01). He showed a good antitumor response and is currently receiving permanent insulin therapy and levothyroxine replacement with the ICI treatment. Based on this case and the available literature, patients with preexisting islet autoantibodies or SPT1DM/LADA, plus a genetic predisposition to T1DM, may have an extremely high risk of developing ICI-related T1DM for a brief period after starting ICI treatment.

Keywords Slowly progressive type 1 diabetes mellitus · Islet autoantibodies · Immune checkpoint inhibitors · Nivolumab · Insulin secretion · Renal cell carcinoma

Introduction

Immune checkpoint inhibitors (ICIs) modulate the immune response via cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), or its ligand (PD-L1) [1]. Patients with several types of advanced cancers have experienced dramatically improved rates of treatment response and survival with ICIs [2], although the reduced immunological tolerance to self-antigens is associated with immune-related adverse events (irAEs) [3]. Endocrine irAEs including thyroid dysfunction, hypophysitis, hypoparathyroidism, adrenal insufficiency, and type 1 diabetes mellitus (T1DM) are unique, relative to other irAEs because they are generally irreversible and do not respond to glucocorticoid treatment [4]. T1DM, a rare but potentially life-threatening endocrine irAE, can lead to diabetic ketoacidosis (DKA) and a permanent requirement for insulin therapy.

Islet autoantibodies are often detected during diagnosis of ICI-related T1DM and include anti-glutamic acid decarboxylase antibodies (GADA), anti-insulinoma-associated antigen 2 antibodies (IA-2A), anti-zinc transporter 8 antibodies (ZnT8A), and insulin autoantibodies (IAA) [5–11]. However, most reports are unclear regarding whether islet

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autoantibodies are present before ICI treatment or develop during the course of ICI treatment. Moreover, the effects of ICI treatment remain unclear among patients with preexisting autoimmune diabetes, such as slowly progressive T1DM (SPT1DM). This is the most prevalent clinical subtype of T1DM in Japan [12] and is also known as latent autoimmune diabetes mellitus in adults (LADA) in other countries [13].

We report a case involving advanced renal cell carcinoma and SPT1DM, and describe the clinical course and insulin secretory capacity before and after ICI treatment.

Case presentation

The patient provided written informed consent for the publication of this case report.

The patient was a 55-year-old Japanese man with a recent diagnosis of SPT1DM and metastatic renal cell carcinoma. His mother had been diagnosed with diabetes; he was diagnosed with type 2 diabetes (at the age of 53 years) and was being treated using oral hypoglycemic agents. Two years later, he experienced visual field impairment and underwent examinations that revealed a right renal tumor with lung and brain metastases. After brain tumor removal, he was referred to our hospital for further examination and treatment.

On admission at our hospital, the patient had a body mass index of 23.4 kg/m^2 (weight: 72.3 kg, height: 175.6 cm) and a waist circumference of 86.0 cm. He had a history of obesity (maximum body mass index: 29.8 kg/m^2 at the age of 51 years) but had lost 10 kg in the previous year. He had no diabetic microvascular complications, and his serum glycated hemoglobin A1c (HbA1c) level was 10.6% with treatment using oral hypoglycemic agents (glimepiride: 3 mg/day, voglibose: 0.9 mg/day, ipragliflozin: 50 mg/day, sitagliptin: 50 mg/day). Post-hospitalization, his glycemic control improved markedly after starting a 1840-kcal diabetic diet. The improvement was likely related to the control of previous overeating habits and preservation of insulin secretory capacity (fasting serum C-peptide: 2.36 ng/mL, plasma glucose: 86 mg/dL, 24-h urinary C-peptide: 186 μg/day). He eventually discontinued the oral hypoglycemic agents and retained good glycemic control (fasting plasma glucose: 110–130 mg/dL, HbA1c: 6.9%). However, despite the treatment for type 2 diabetes mellitus, he was newly diagnosed with SPT1DM based on serum GADA positivity (114 U/mL; normal range < 5.0 U/mL). Furthermore, despite being biochemically euthyroid, he was diagnosed with autoimmune thyroiditis based on positivity for thyroglobulin antibodies (Tg-Ab) and thyroid peroxidase antibodies (TPO-Ab).

Based on the good glycemic control without the use of hypoglycemic agents, the patient underwent right nephrectomy, and the pathological diagnosis was renal cell carcinoma with lung and brain metastases. After surgery, he maintained good glycemic control without the use of hypoglycemic agents, based on a fasting plasma glucose level of 95–130 mg/dL and HbA1c level of 6.3%. He received the first ICI treatment (nivolumab (a PD-1 inhibitor) plus ipilimumab (a CTLA-4 inhibitor)) without any acute complications. However, 17 days post-ICI treatment initiation, he visited our hospital with a 5-day history of excessive sweating, diarrhea, and fever. Endocrinological examination revealed thyrotoxicosis (thyroid-stimulating hormone: 0.01 μU/mL, free thyroxine: > 5.00 ng/dL, free triiodothyronine: > 20 pg/mL) but no thyrotropin receptor antibodies, although incremental increases were detected in his serum Tg-Ab and TPO-Ab levels relative to the pre-ICI treatment levels (Tg-Ab: 45.7 → 673 IU/mL; normal range < 4.11 IU/mL, TPO-Ab: 133 → 710 IU/mL; normal range < 5.61 IU/mL). On the other hand, his glycemic control remained relatively stable (casual plasma glucose level, 230 mg/dL; HbA1c level, 6.3%). Therefore, he was diagnosed with destructive thyroiditis following ICI treatment, and the second ICI treatment cycle was delayed once. At day 24 post-ICI treatment initiation, the thyrotoxicosis appeared to spontaneously improve. Although his HbA1c level increased to 6.7%, his insulin secretory capacity was preserved: casual C-peptide level, 7.38 ng/mL and corresponding plasma glucose level, 187 mg/dL.

On day 38 post-ICI treatment initiation, he was admitted at another hospital to undergo CyberKnife treatment for brain metastasis. On admission, he reported polydipsia, and his casual plasma glucose level was markedly elevated (857 mg/dL). Thus, he received intravenous rehydration and insulin, plus a subcutaneous insulin injection, in addition to the CyberKnife treatment. The next day, he was re-admitted to our hospital because of hyperglycemia. His consciousness was clear; his body mass index was 21.2 kg/m^2 (weight: 64.3 kg), corresponding to a weight loss of 7.0 kg relative to that pre-ICI treatment. There were no abnormal physical signs: blood pressure, 104/78 mmHg; pulse rate, 100 bpm; and body temperature, 36.8℃. Laboratory findings are shown in Table 1. The casual plasma glucose level improved slightly (482 mg/dL); the total ketone body level was not excessively high (769 μM/L), with no metabolic acidosis, likely related to the treatment at the previous hospital. However, in just 17 days, his HbA1c level had increased markedly from 6.7 to 9.8%, with a plasma glucose level of 189 mg/dL and markedly decreased fasting serum C-peptide (0.26 ng/mL) and 24-h urinary C-peptide (1.3 μg/day) levels. Furthermore, the glucagon loading test revealed severe pancreatic β-cell impairment with a delta C-peptide response of 0.06 ng/mL. The GADA level increased markedly from 114 U/mL pre-ICI treatment to 1160 U/mL; he tested positive for IA-2 antibodies (> 30 U/mL; normal range, < 0.6 U/mL). Interestingly, human leukocyte antigen (HLA) typing

Table 1 Patient's laboratory data from the time of admission

Blood chemistry		*Antibodies*	
Glucose	482 (mg/dL)	GADA	1160 (U/mL)
C-peptide	0.44 (ng/mL)	IA-2A	> 30 (U/mL)
Glycated hemoglobin	9.8 (%)	IAA	< 125 (nU/mL)
Blood urea nitrogen	22.9 (mg/dL)	Tg-Ab	341 (IU/mL)
Creatinine	1.09 (mg/dL)	TPO-Ab	1360 (IU/mL)
eGFR	55.9 (mL/min/1.73 m^2)	*Endocrine examination*	
Sodium	132 (mEq/L)	ACTH	27.6 (pg/mL)
Potassium	4.4 (mEq/L)	Cortisol	11.9 (μg/dL)
Chloride	98 (mEq/L)	DHEA-S	162 (μg/dL)
Amylase	79 (IU/L)	TSH	24.13 (μU/mL)
Lipase	39 (U/L)	Free T3	< 1.5 (pg/mL)
Elastase-1	101 (ng/dL)	Free T4	0.47 (ng/dL)
Acetoacetic acid	224 (μM/L)	GH	3.29 (ng/mL)
3-hydroxybutyric acid	545 (μM/L)	IGF-1	155 (ng/mL)
Total ketone body	769 (μM/L)	LH	3.54 (mIU/mL)
Venous blood gas analysis		FSH	11.81 (mIU/mL)
pH	7.335	Free testosterone	6.4 (pg/mL)
HCO_3^-	22 (mmol/L)	Prolactin	13.08 (ng/mL)
Base excess	– 3.7 (mmol/L)	*HLA typing analysis*	
Urinalysis		DRB1*08:03/09:01	
24-h urinary C-peptide	1.3 (μg/day)	DQB1*03:03/06:01	
Glucagon loading test			
(before loading)		(6 min after loading)	
C-peptide	0.17 (ng/mL)	C-peptide	0.23 (ng/mL)
Glucose	196 (mg/dL)	Glucose	202 (mg/dL)

eGFR estimated glomerular filtration ratio, *GADA* anti-glutamic acid decarboxylase antibody, *IA-2A* anti-insulinoma-associated antigen 2 antibody, *IAA* insulin autoantibodies, *Tg-Ab* anti-thyroglobulin antibody, *TPO-Ab* anti-thyroid peroxidase antibody, *ACTH* adrenocorticotropic hormone, *DHEA-S* Dehydroepiandrosterone sulfate, *TSH* thyroid-stimulating hormone, *Free T3* free triiodothyronine, *Free T4* free thyroxine, *GH* growth hormone, *IGF-1* insulin growth factor-1, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *HLA* human leukocyte antigen

identified a haplotype indicating susceptibility to T1DM (DRB1*09:01–DQB1*03:03) [14]. Endocrinological findings did not suggest hypopituitarism or adrenal insufficiency but indicated hypothyroidism following destructive thyroiditis. Chest computed tomography (CT) revealed a marked reduction in metastatic lung tumor size.

We judged that his insulin secretory capacity in SPT1DM had drastically reduced for a brief period after destructive thyroiditis, caused by a single ICI treatment cycle. However, the patient did experience a good reduction in tumor burden. Thus, he was immediately started on intensive insulin therapy and levothyroxine replacement; ICI treatment was resumed after improved glycemic control. His serum C-peptide levels were undetectable at 10 months post-ICI treatment initiation, and he has continued intensive insulin therapy (insulin degludec 3 units daily plus insulin aspart with carbohydrate counting; insulin to carbohydrate ratio: breakfast: 2.8, lunch: 9.5, dinner: 8.5; insulin sensitivity factor: 30) and levothyroxine replacement (100 μg/day). Chest CT confirmed a significant treatment response with further reduction in the size of lung metastases during ICI treatment.

Discussion

We encountered a patient with advanced renal cell carcinoma and SPT1DM who experienced drastically reduced insulin secretory capacity for a brief period after only one cycle of treatment using PD-1 and CTLA-4 inhibitors. To the best of our knowledge, this is the first report describing the clinical course and insulin secretory capacity before and after ICI treatment in a patient with SPT1DM.

The estimated incidence of ICI-related T1DM is approximately 1% [5–11]. Most cases of ICI-related T1DM are attributed to anti-PD-1/PD-L1 monotherapy or anti-PD-1 plus anti-CTLA-4 combination therapy, as in this case. Cases attributed to anti-CTLA-4 monotherapy are extremely rare, and almost all cases involved PD-1 inhibitor and/or

interferon treatment before CTLA-4 inhibitor [6]. The predominance of PD-1/PD-L1 inhibitors, rather than CTLA-4 inhibitors, as the causative agent, may be related to their frequency of use and indications. However, it may also indicate that PD-1/PD-L1 pathway is important for the tolerance of pancreatic β-cell antigens and the pathogenesis of ICI-related T1DM.

Islet autoantibodies are detected in 5 to 71% of patients who present with ICI-related T1DM [5–11] and can be used as a prediction or diagnostic markers of T1DM, including SPT1DM/LADA [15]. Furthermore, > 90% of patients who develop T1DM have islet autoantibodies before diagnosis [16], and an increasing number of islet autoantibodies is related to an increasing likelihood of developing T1DM [17]. Moreover, high GADA titers are associated with insulin dependency risk in patients with SPT1DM/LADA [18, 19]. However, the prevalence of islet autoantibodies in patients with ICI-related T1DM may differ from those in patients with classic T1DM and SPT1DM/LADA (islet autoantibodies are present in almost all cases) or fulminant T1DM (islet autoantibodies are rarely present). Mechanisms underlying the difference in islet autoantibodies between spontaneous-onset and ICI-related T1DM are unclear, although the presence of islet autoantibodies in patients with ICI-related T1DM may be related to ethnicity. For example, in a study in Japan, where fulminant T1DM is common, islet autoantibodies were not detected in 21 of 22 patients with ICI-related T1DM [7].

It is also unclear whether islet autoantibodies are present before ICI treatment or develop during ICI treatment, as most studies failed to perform the related tests before starting ICI treatment. The few reports that described related testing revealed a mix of patients who showed positivity before ICI treatment or seroconversion after treatment [9, 20, 21]. Similar to our case, 3 cases involved positivity for islet autoantibodies before ICI treatment, and detailed characteristics were reported for 2 cases (Table 2). All 3 patients were treated using nivolumab monotherapy and had no history of diabetes before PD-1 inhibitor treatment, unlike in our case. However, it is very interesting that an extremely short period was observed between PD-1 inhibitor treatment initiation and ICI-related diabetes onset (Case 1: 6 weeks and 3 cycles, Case 2: 4 weeks and 2 cycles, our case: 5 weeks and 1 cycle). In general, the time from starting ICI treatment to T1DM

Table 2 Characteristics of reported patients with ICI-related T1DM and preexisting islet autoantibodies before ICI treatment

	Case 1 [Ref. 21]	Case 2 [Ref. 20]	Our case
Age (years)	73	34	55
Sex	Male	Female	Male
BMI (kg/m^2)	28	NA	21.2
Neoplasia	Melanoma	Non-small cell lung cancer	Renal cell carcinoma
History of diabetes before ICI treatment	No	No	Yes (SPT1DM)
ICIs	Nivolumab	Nivolumab	Nivolumab + ipilimumab
Clinical T1DM subtype	Acute onset type	Fulminant type	Acute onset type
Time and cycles to onset	6 weeks and 3 cycles	4 weeks and 2 cycles	5 weeks and 1 cycle
Blood glucose (mg/dL)	500	739	482*
Glycated hemoglobin (%)	8.8	7.1	9.8*
Ketoacidosis	Yes	Yes	No*
CPR value before and after ICI treatment (ng/mL)	1.19 → not detectable	NA → < 0.1	2.36 → 0.26
Islet antibodies before ICI treatment	GADA > 2000 IU/L IA-2A 15 U/mL ZnT8A 463 U/mL	GAD-65A(RIA) > 250 U/L IA-2A 6.2 U/mL ZnT8A 64 U/mL IAA < 0.4 U/mL	GADA 114 U/L
Islet antibodies at the presentation of ICI-related T1DM	GADA > 2000 IU/L IA-2A 27 U/mL ZnT8A 802 U/mL	GAD-65A(ELISA) > 30 U/L IA2A 6.1 U/mL IAA 0.4 U/mL	GADA 1160 U/L IA-2A > 30 U/mL IAA < 125 nU/mL
HLA typing	NA	A*30:01/30:02, DR9	DRB1*08:03/09:01 DQA1*01:03/03:01 DQB1*03:03/06:01
Other autoimmune disease	No	No	Thyroiditis

ICI immune checkpoint inhibitor, *BMI* body mass index, *T1DM* type 1 diabetes mellitus, *SPT1DM* slowly progressive type 1 diabetes mellitus, *GADA* anti-glutamic acid decarboxylase antibody, *GAD-65A* anti-glutamic acid decarboxylase-65 antibody, *IA-2A* anti-insulinoma-associated antigen 2 antibody, *ZnT8A* anti-zinc transporter 8 antibody, *IAA* insulin autoantibodies, *HLA* human leukocyte antigen, *Ref* reference number, *NA* not assessed

*Data after insulin treatment at the previous hospital

diagnosis varied from 1 week to 1 year (median: 7 weeks) [5]. Moreover, the time to diabetes onset for patients with islet autoantibodies at presentation is significantly shorter than for islet autoantibody-negative patients (7 weeks vs. 16 weeks) [5]. Thus, patients with preexisting islet autoantibodies before ICI treatment will likely have a short time to T1DM onset (mean duration: 5 weeks and 2 cycles in our case and the 2 cases with detailed information). Moreover, preexisting thyroid autoantibodies before ICI treatment are associated with the early development of thyroid dysfunction, which can be an endocrine irAE [22]. Therefore, we speculate that patients with preexisting islet autoantibodies or SPT1DM/LADA are more likely to develop ICI-related T1DM relatively quickly after starting ICI treatment. On the other hand, Ohara et al. have reported a patient with preexisting IA-2A (0.8 U/mL; reference range: < 0.4 U/mL) who developed non-insulin-dependent diabetes (casual blood glucose: 328 mg/dL, HbA1c: 6.4%) without ketosis after starting nivolumab [23]. However, this patient's endogenous insulin secretion capacity was preserved at the diagnosis (CPR: 6.5 ng/mL) and for > 1 year without anti-diabetic medication (CPR: 8.7 ng/mL). Thus, this case may not fall under the category of ICI-related T1DM with reduced insulin secretion capacity. In addition, that case involved negative results for most islet autoantibodies, including GADA, IAA, ZnT8A, and islet cell antibodies, with the exception of IA-2A. In cases with only IA-2A positivity, there is an extremely low ability to predict the development of T1DM in first-degree relatives and most patients fail to develop β-cell failure in SPT1DM/LADA [18, 24, 25]. Therefore, we speculate that cases with only IA-2A positivity may be less likely to develop ICI-related T1DM.

Our case involved an HLA haplotype (DRB1*09:01–DQB1*03:03) that indicated susceptibility to T1DM, detected in approximately 70–80% of patients with ICI-related T1DM and its prevalence is estimated to be comparable to or higher than patients with spontaneous-onset T1DM [5–11, 26]. Patients with islet autoantibodies and susceptible HLA haplotypes also have a short time between starting PD-1 inhibitor treatment and ICI-related T1DM detection, relative to patients with only islet autoantibodies [5]. These findings suggest that susceptible HLA haplotypes may shorten the time to T1DM onset. Interestingly, our case also involved a protective haplotype (DRB1*08:03–DQB1*06:01) for T1DM [27]. A few reports have indicated that 16–30% of patients with ICI-related T1DM have protective HLA types and that some but not all of these patients also had susceptible HLA types, as in our case [6, 10]. This haplotype in our case (DRB1*08:03–DQB1*06:01) is also linked to autoimmune thyroid disease susceptibility [27].

Our patient developed destructive thyroiditis concomitant with T1DM after ICI treatment. Stamatouli et al. reported that 70% of patients with ICI-related diabetes (19/27 cases) had other irAEs and 44% of these patients (12/27 cases) had an endocrine irAE before, or concomitant with the development of diabetes, and that thyroid dysfunction was the most common endocrine irAE (11/12 cases) [9]. The prevalence of thyroid irAEs is classified according to the presence or absence of thyroid autoantibodies (Tg-Ab or TPO-Ab) before ICI treatment, and positivity for thyroid autoantibodies before ICI treatment is associated with a significantly increased risk of thyroid irAEs [28]. Furthermore, patients with preexisting autoimmune diseases have more irAEs than patients without autoimmune diseases [29]. Therefore, patients with islet autoantibodies or SPT1DM/LADA before ICI treatment may have an extremely high risk of ICI-related T1DM, with a short interval between starting ICI treatment and developing T1DM. In these cases, monitoring of blood glucose levels after starting ICI treatment may be crucial for the early detection of ICI-related T1DM and the prevention of DKA.

Our patient had a good antitumor response to ICI treatment; as reported, patients who develop irAEs have an increased likelihood of good antitumor response and long survival [30, 31]. Interestingly, as in our case, ICI-related T1DM may be associated with good tumor response [9, 10]. However, further studies are needed to confirm whether patients with islet autoantibodies or SPT1DM/LADA before ICI treatment have a better antitumor response to that treatment.

Our report has several limitations. First, the existence of DKA at ICI-related T1DM onset could not be proven, as blood gas analysis and ketone body testing results from the previous hospital were lacking. Second, we did not examine islet autoantibodies except for GADA before ICI treatment and ZnT8A after ICI treatment. However, our findings may contribute to DKA prevention and to elucidating the predictors and pathophysiology of ICI-related T1DM.

In conclusion, we encountered a patient with preexisting SPT1DM and HLA haplotypes that indicated susceptibility to T1DM. The patient experienced a drastic reduction in his insulin secretory capacity for a brief period after only one cycle of treatment using PD-1 and CTLA-4 inhibitors. Further studies are needed to identify the risk factors for ICI-related T1DM, although clinicians should be aware that patients with preexisting islet autoantibodies or SPT1DM/LADA, plus a genetic predisposition to T1DM, may have an extremely high risk of developing ICI-related T1DM for a brief period after starting ICI treatment.

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Compliance with ethical standards

Conflicts of interest Tetsuyuki Yasuda has received lecture fees from Takeda Pharmaceutical Company Limited, Novartis Pharmaceuticals Corp., and Nippon Boehringer Ingelheim Co., Ltd. The other authors declare that they have no conflicts of interest.

Human rights statement and informed consent All procedures were approved by the appropriate institutional review board (the Ethics Committee of Osaka Police Hospital, approved April 28, 2020, approval number: 1190) and complies with the Declaration of Helsinki and its amendments. Informed consent was obtained from the patient for the publication of this case report.

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