Immune checkpoint inhibitor-related type 1 diabetes mellitus with closely monitored dynamics of glutamic acid decarboxylase antibody levels before and after disease onset: a case report

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Abstract

Immune checkpoint inhibitor (ICI)-related type 1 diabetes mellitus (T1DM) is a severe immune-related adverse event (irAE), occurring in < 1% of cases. ICI-related T1DM typically progresses more rapidly than conventional acute-onset T1DM, but is slower than conventional fulminant T1DM, suggesting different processes of onset and progression. Positivity rates for glutamic acid decarboxylase (GAD) antibodies differ, with ICI-related T1DM showing a lower positivity rate than conventional acute-onset T1DM. However, no detailed follow-up studies have examined the GAD antibody levels before and after the onset of ICI-related T1DM. We report the case of a 58-year-old Japanese man with type 2 diabetes mellitus diagnosed with renal carcinoma and multiple lung metastases. Chemotherapy with pembrolizumab (an anti-programmed death-1 antibody) was initiated. On the first day of treatment, the patient's insulin secretion capacity was preserved, and GAD antibodies were negative. Thirty-four days after chemotherapy initiation, the patient developed diabetic ketoacidosis and was diagnosed with ICI-related T1DM. Interestingly, GAD antibodies became positive (17.7 U/mL) approximately one month after the initial ICI administration. Subsequently, GAD antibody levels declined rapidly, with negative conversion occurring in only 205 days (approximately 6.5 months). To the best of our knowledge, this is the first reported case of closely monitoring GAD antibody dynamics before and after the onset of ICI-related T1DM. Here, the dynamics of the GAD antibodies were clearly distinct from those in conventional acute-onset T1DM. This case report may provide valuable insights into the differences between the autoimmune responses of ICI-related and conventional T1DM in their disease onset and progression.

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Keywords: immune checkpoint inhibitors, immune checkpoint inhibitor-related type 1 diabetes mellitus, acute-onset type 1 diabetes mellitus, fulminant type 1 diabetes mellitus, glutamic acid decarboxylase antibody

Introduction

Immune checkpoint inhibitors (ICIs), which modulate immune responses, significantly impact the field of oncology and are currently being used to treat various cancers [1]. Although ICIs significantly improve cancer prognosis and survival, they can cause immune-related adverse events (irAEs). Among these, ICI-related type 1 diabetes mellitus (T1DM) is a severe irAE, occurring in < 1% of cases [2]. With the increasing use of ICIs, reports of ICI-related T1DM, which is recognized as a new disease entity, have been increasing [3]. ICI-related T1DM tends to progress more rapidly than conventional acute-onset T1DM but more slowly than conventional fulminant T1DM [4], suggesting different processes of onset and progression. The positivity rates of glutamic acid decarboxylase (GAD) antibodies differ, with ICI-related T1DM showing a lower positivity rate than conventional acute-onset T1DM in Japan and Western countries [5–7]. However, no detailed follow-up studies on GAD antibody levels before and after the onset of ICI-related T1DM have been reported.

Here, we present the first case of a patient with closely monitored dynamics of GAD antibody levels before and after the onset of ICI-related T1DM.

Case report

A 58-year-old Japanese man was admitted to our department for treatment of diabetic ketoacidosis (DKA). He was diagnosed with type 2 diabetes mellitus (T2DM) at 42 years of age and treated with oral hypoglycemic agents. At 51 years of age, he underwent left nephrectomy for left renal carcinoma. At 55 years of age, a solitary lung metastasis was discovered, and a left upper lobectomy was performed. However, during follow-up, multiple lung metastases were found, and at 57 years of age, chemotherapy was initiated with combined pembrolizumab (an anti-programmed death-1 antibody) and

lenvatinib (a tyrosine kinase inhibitor). Laboratory findings on the first day of treatment showed high hemoglobin A1c (HbA1c; 8.1%), despite using oral hypoglycemic agents (metformin; 1000 mg/day, teneligliptin; 20 mg/day, voglibose; 0.6 mg/day). The patient's fasting plasma glucose level was 191 mg/dL and serum C-peptide level was 2.3 ng/mL, indicating preserved insulin secretion capacity. The patient tested negative for GAD antibodies. After the second chemotherapy infusion, the patient suddenly developed thirst, polydipsia, polyuria, and generalized fatigue that gradually worsened. The patient visited our hospital on the third day of the second dose (34 days after treatment initiation).

Upon arrival, he displayed a slight decrease in consciousness and scored 13 points (E3V4M6) on the Glasgow coma scale. The patient's body mass index was 26.5 kg/m^2 (70.4 kg), and he presented with elevated blood pressure (157/86 mmHg) and sinus tachycardia (107 beats/min). Physical examination revealed no remarkable signs, excluding dry mouth. Laboratory findings (Table 1) revealed an excessively high casual plasma glucose level of 850 mg/dL and elevated HbA1c level of 10.5%. Venous blood gas analysis revealed high anion gap metabolic acidosis (pH; 7.168, pCO_2; 29.9 mmHg, HCO_3^-; 10.8 mEq/L, anion gap; 31.2 mEq/L). The urine was positive for ketone bodies. Accordingly, the patient was diagnosed with DKA and admitted to our department. Intravenous rehydration and insulin therapy were initiated. Among the pancreatic exocrine enzymes, only serum lipase level was elevated (123 U/L). Interestingly, GAD antibodies, which were negative before chemotherapy, became positive in 34 days (17.7 U/mL), whereas other anti-islet autoantibodies were negative. The patient's datasets after recovery from DKA revealed significantly declined serum C-peptide levels (< 0.1 ng/mL) and 24-h urinary C-peptide levels (1.15 μg/day). Additionally, the ΔC-peptide after glucagon stimulation test was undetectable, indicating complete depletion of insulin secretion capacity. Based on the development of ketoacidosis approximately 3 days after

the onset of hyperglycemic symptoms and complete insulin depletion, the patient fulfilled the diagnostic criteria for fulminant T1DM, as established by the committee of the Japanese Diabetes Society [8]. The HbA1c criterion (HbA1c < 8.7%) was not applicable because of previously treated T2DM. Human leukocyte antigen typing identified a haplotype indicating susceptibility to T1DM (DRB1-DQB1 **04:05-*04:01*) [9]. Endocrinological examinations showed no abnormalities, excluding subclinical hypothyroidism, which was treated with levothyroxine sodium 25 μg/day. Antithyroglobulin and antithyroid peroxidase antibody tests were negative. We concluded that the patient developed ICI-related T1DM during T2DM and initiated multiple insulin injections.

The time course of GAD antibody levels is shown in Figure 1. After discharge, GAD antibody levels declined rapidly, with negative conversion occurring in only 205 days (approximately 6.5 months). Chemotherapy was resumed for renal carcinoma with multiple metastases, resulting in a partial response, as evidenced by a 44% reduction in the size of the metastatic lesions on chest computed tomography.

Discussion

We present the case of a patient who developed ICI-related T1DM during follow-up for T2DM and renal carcinoma with multiple lung metastases. The patient's GAD antibodies became positive approximately one month after the initial ICI administration, coinciding with the onset of ICI-related T1DM. The antibodies rapidly declined and became negative after 205 days. While several reports have shown positive conversions of anti-islet autoantibodies with the onset of ICI-related T1DM [10-12], there have been no reports of detailed follow-up of GAD antibody levels thereafter. To the best of our knowledge, this is the first reported case of closely monitoring GAD antibody dynamics

before and after the onset of ICI-related T1DM.

Although the exact mechanisms behind the production of anti-islet autoantibodies remain unclear, it is assumed that they are produced in response to autoantigens released from β-cells damaged by immune cells, mainly cytotoxic T lymphocytes, which are activated by triggers, such as viral infections [5, 13]. These autoantibodies do not directly harm the β-cells but rather appear as a consequence of β-cell damage and may emerge in the blood 7–20 days after the initial trigger [5, 13]. Among these autoantibodies, GAD antibodies showed the highest positivity rate [14].

Although GAD antibodies are used to predict or diagnose T1DM [5, 15], their dynamics may differ between conventional and ICI-related T1DM. First, the positivity rates of GAD antibodies at the onset of T1DM vary among the T1DM subtypes. In conventional acute-onset T1DM, GAD antibodies are positive in 60–80% of patients [5], whereas in conventional fulminant T1DM, they are positive in only 4.8–12.1% [16, 17]. For ICI-related T1DM, the positivity rate is 4.8% in Japan [6] and 40–50% in Western countries [18], which is clearly lower than that in conventional acute-onset T1DM and comparable to that in conventional fulminant T1DM in Japan. Second, the time from the appearance of GAD antibodies to the onset of T1DM in conventional acute-onset T1DM spans several years [19, 20]. However, there have been no reports on this interval for conventional fulminant T1DM and ICI-related T1DM. Here, the interval was only one month. Third, the duration of GAD antibody persistence after the onset of T1DM is > 5 years in many patients with conventional acute-onset T1DM [21]. For conventional fulminant T1DM, the exact duration is unclear, although there is only one report of GAD antibodies becoming undetectable within two years [17]. There are no reports on the persistence of GAD antibodies in ICI-related T1DM. The patient's GAD antibody levels were undetectable after 205 days. These findings suggest that the dynamics of GAD

antibodies differ between ICI-related and conventional T1DM, especially acute onset, considering the different autoimmune responses in disease onset and progression. The rapid appearance and negative conversion of GAD antibodies in our patient may reflect the sudden onset and progression of β-cell damage and subsequent rapid depletion of autoantigens in β-cells. Actually, the patient developed DKA rapidly, and his insulin secretion capacity was significantly reduced at the onset of T1DM. Furthermore, our recent report of histopathological analyses in patients with ICI-related T1DM has shown that β-cells were almost completely absent even one month after the onset of T1DM [22]. GAD antibody levels of the patient were > 2,000 U/mL at the onset, but follow-up data were not available [22]. Therefore, in GAD antibody-positive ICI-related T1DM, monitoring GAD antibody dynamics may be helpful in estimating the progression of β-cell damage. Conversely, there is limited evidence regarding the trends in GAD antibodies in conventional fulminant T1DM. Provided that the clinical course of this case was consistent with that of conventional fulminant T1DM, whether GAD antibody trends differ between ICI-related and conventional fulminant T1DM remains unclear.

Among patients with ICI-related T1DM, those who are autoantibody-positive at diagnosis have a shorter time from ICI administration to disease onset than those who are autoantibody negative [18]. Additionally, autoantibody-positive patients have a higher risk of presenting with DKA, are more likely to show elevated lipase levels, and have a higher prevalence of preexisting T2DM than autoantibody-negative patients [18]. These characteristics are consistent with our patient's clinical profile. However, the underlying reasons for these differences remain unclear, and further research is required to better understand the differences between patients with and without autoantibodies.

In conclusion, we encountered a patient whose GAD antibody levels changed dramatically before and after the onset of ICI-related T1DM with dynamics that were

clearly different from those of conventional acute-onset T1DM. Since this is only a single report and > 50% of the ICI-related T1DM cases are GAD antibody-negative, it may not fully represent the disease process in ICI-related T1DM. Nevertheless, this case report may provide valuable insights into the differences between the autoimmune responses of ICI-related and conventional T1DM in their disease onset and progression. Further accumulation of precise case studies is essential.

Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed.

Compliance with Ethical Standards

This article does not contain any studies with human or animal subjects performed by any of the authors.

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None

Disclosure of potential conflicts of interest

The authors declare no conflicts of interest.

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Figure legends

Fig. 1. The time course of GAD antibody levels and diabetic parameters

GAD antibodies became positive 34 days after initial ICI administration. The antibodies rapidly declined and became negative after 205 days.

ICI, immune checkpoint inhibitor; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; GAD, glutamic acid decarboxylase

Table 1. Laboratory findings of the patient after admission

Hematologic characteristics (day 0)			**Venous blood gas analysis (day 0)**		
WBC	7170 /μL	(3300–9400)	pH	7.168	
RBC	5.65×10^6 /μL	($3.9–5.1\times10^6$)	CO_2	29.9 mmHg	
Hemoglobin	18.7 g/dL	(12.0–15.0)	HCO_3^-	10.8 mEq/L	
Platelet	116×10^3 /μL	($130–320\times10^3$)	Base excess	-16.2 mEq/L	
Biochemical characteristics (day 0)			Anion gap	31.2 mEq/L	
Sodium	128 mEq/L	(138–145)	**Urinalysis findings (day 0)**		
Potassium	6.7 mEq/L	(3.6–4.8)	Protein	1+	
Chloride	86 mEq/L	(100–108)	Glucose	4+	
Urea nitrogen	53 mg/dL	(7–22)	Ketone bodies	2+	
Creatinine	2.05 mg/dL	(0.5–0.9)	**Endocrinological characteristics (day 2)**		
eGFR	27.6 mL/min/1.73m^2		TSH	7.99 μIU/mL	(0.61–4.23)
Albumin	4.3 g/dL	(3.6–4.7)	FT4	1.2 ng/dL	(0.8–1.7)
AST	13 U/L	(<40)	FT3	1.8 pg/mL	(2.1–3.1)
ALT	24 U/L	(<40)	TgAb	<5.0 IU/mL	(<5.0)
γ-GTP	23 U/L	(12–69)	TPOAb	<3.0 IU/mL	(<3.0)
LDH	277U/L	(124–222)	ACTH	31 pg/mL	(7–63)
Amylase	78 U/L	(44–153)	Cortisol	12 μg/dL	(4.0–18.3)
Lipase	123 U/L	(9–52)	**Glucagon stimulation test (day 17)**		
Elastase-1	198 ng/dL	(0–300)	FPG	159 mg/dL	(70–110)
C-reactive protein	0.37 mg/dL	(0.0–0.2)	C-peptide (0 min)	<0.1 ng/mL	
Plasma glucose	850 mg/dL	(70–110)	C-peptide (6 min)	<0.1 ng/mL	
Hemoglobin A1c	10.5%	(4.6–6.2)	**Urinalysis findings (day 8, 9)**		
Glycoalbumin	40.5%	(11.0–16.0)	Urinary C-peptide	1.15 μg/day	(48.7–97.7)
GAD antibodies	17.7 U/mL	(<5)	Urinary albumin	201.7 mg/day	
IA-2 antibodies	<0.6 U/mL	(<0.6)	**HLA typing**		
IAA	<0.4 U/mL	(<0.4)	DRB1-DQB1	**04:05-*04:01/*09:01-*03:02*	
ZnT8 antibodies	<10 U/mL	(<15.0)			

Reference ranges are shown in parentheses.

WBC, white blood cell count; RBC, red blood cell count; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; GAD antibodies, glutamic acid decarboxylase antibodies; IA-2 antibodies, insulinoma-associated protein-2 antibodies; IAA, insulin autoantibodies; ZnT8 antibodies, zinc transporter 8 antibodies; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free 3,5,3′-triiodothyronine; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; ACTH, adrenocorticotropic hormone; FPG, fasting plasma glucose; HLA typing, human leukocyte antigen typing