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【 CASE REPORT 】

A Patient with Nivolumab-related Fulminant Type 1 Diabetes Mellitus whose Serum C-peptide Level Was Preserved at the Initial Detection of Hyperglycemia

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Abstract:
A 77-year-old-man with renal cell carcinoma who was undergoing nivolumab treatment visited our department due to hyperglycemia; his plasma glucose level was 379 mg/dL. Although his serum C-peptide immunoreactivity (CPR) level was preserved (5.92 ng/mL), we suspected an onset of fulminant type 1 diabetes mellitus (FT1DM) and immediately started insulin therapy. His CPR levels gradually decreased and were depleted within 1 week. We later discovered that the patient's casual CPR level had been abnormally high (11.78 ng/mL) 2 weeks before his admission. Hence, the possibility of FT1DM in hyperglycemic patients undergoing nivolumab treatment should not be excluded, even with a preserved CPR level.

Key words: nivolumab, fulminant type 1 diabetes mellitus, anti-PD-1 antibody

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Introduction

Immune checkpoint inhibitors, such as anti-programmed cell death 1 (PD-1) antibodies, are increasingly being used as anticancer drugs. However, these antibodies can cause immune-related adverse events, including type 1 diabetes mellitus (T1DM) through their activation of autoreactive T cells (1). Nivolumab-related T1DM reportedly manifests as fulminant type 1 diabetes mellitus (FT1DM), which is an emergency condition because patients develop ketosis or ketoacidosis within approximately 1 week. The fasting serum C-peptide immunoreactivity (CPR) level of patients with FT 1DM is usually <0.3 ng/mL (2) because the insulin secretion capability is destroyed immediately after the disease onset. Thus, clinicians may inadvertently rule out the possibility of FT1DM in hyperglycemic patients with preserved CPR levels. We herein report the case of a patient with nivolumab-related FT1DM who presented with a preserved serum CPR level at the onset of hyperglycemia.

Case Report

A 77-year-old Japanese man who was undergoing nivolumab treatment (3 mg/kg, once every 2 weeks) was referred to the endocrinology department of our hospital after developing hyperglycemia. He had no personal or family history of diabetes. He was being treated with nivolumab at our oncology department after previous courses of sunitinib, everolimus, axitinib, and pazopanib for renal cell carcinoma with lung metastasis. Despite receiving 4 lines of anti-cancer drugs, the patient developed progressive disease, which led to the prescription of nivolumab. No glucose intolerance was noted at that time; his casual blood glucose and glycated hemoglobin (HbA1c) levels were 112 mg/dL and 5.4%, respectively. On day 15 of the 6th cycle of nivolumab infusion, a blood test revealed hyperglycemia with a casual plasma glucose level of 379 mg/dL, whereupon he was re-

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Table 1. The Patient's Laboratory Data on Admission.

Parameter	Value	Unit	Parameter	Value	Unit
TP	8	g/dL	WBC	8,800	/μL
ALB	4.1	g/dL	Neut	42	%
AST	30	U/L	Lymph	24	%
ALT	27	U/L	Mono	7	%
ALP	291	U/L	Basophil	0	%
LDH	257	U/L	Eosinophil	19	%
γ-GTP	26	U/L	HGB	12.1	g/dL
T-Bil	0.8	mg/dL	PLT	24.3	$\times 10^4$/μL
UA	6.6	mg/dL			
BUN	25.1	mg/dL	Venous blood gas analysis		
CK	455	U/L	pH	7.42	
CRE	1.21	mg/dL	PCO_2	36.8	mmHg
Na	132	mEq/L	pO_2	49	mmHg
K	4.9	mEq/L	HCO_3^-	23.9	mmol/L
Cl	99	mEq/L			
Ca	9.3	mg/dL	Urinary analysis		
CRP	0.25	mg/dL	Protein	(±)	
AMY	129	U/L	Glucose	(4+)	
Elastase 1	406	ng/dL	Ketone	(-)	
Lipase	148.1	U/L			
PG	379	mg/dL			
HbA1c	6.2	%			
GA	18.9	%			

TP: total protein, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyltranspeptidase, T-Bil: total bilirubin, UA: urine acid, BUN: blood urea nitrogen, CK: creatine kinase, CRE: creatinine, CRP: C-reactive protein, AMY: amylase, PG: plasma glucose, HbA1c: glycated hemoglobin, GA: glycated albumin, WBC: white blood cell count, HGB: hemoglobin, PLT: platelet

ferred to our department. Although his insulin secretion appeared to be preserved with a serum CPR level of 5.92 ng/mL, a diabetologist suspected the onset of FT1DM. The patient was hospitalized at our department the following day.

The patient's consciousness was clear. A physical examination revealed the following findings: body temperature, 36.5°C; blood pressure, 130/72 mmHg; pulse rate, 73 bpm; and respiratory rate, 16/min. He was 172.2 cm tall and his body weight was 65.5 kg (body mass index, 22.1 kg/m^2). There were no abnormal findings on the patient's head, face, neck, chest, or abdomen and no neurological abnormalities were detected.

The patient's laboratory data are shown in Tables 1 and 2. A urinary glucose was strongly positive, while a urinary ketone test was negative. Although the patient's casual blood glucose level was markedly high (379 mg/dL), his HbA1c level was 6.2%; furthermore, elastase 1 was the only elevated pancreatic enzyme. While the patient's fasting serum CPR level was not depleted on the 2nd day of hospitalization (2.97 ng/mL), the secretion of additional insulin during meal tolerance and glucagon loading tests appeared to be impaired. All pancreatic islet-associated autoantibodies, including anti-GAD antibody, were negative, and endocrinological testing revealed no abnormal findings. Furthermore, there were no increases in virus titers. His HLA-DNA type was HLA-DRB1* 09:01:02/12:01:01, HLA-DQB1* 03:01:01/03:03:02, HLA-DPB1* 05:01:01, and HLA-DQA1* 03:02/05:05. Imaging examinations revealed no evidence of infection or morphological abnormalities in the pancreas.

Although the serum CPR level appeared to be preserved, we considered the possibility of nivolumab-related FT1DM because there was no other explanation for the patient's hyperglycemia. Thus, we commenced intensive insulin therapy immediately after hospitalization. As shown in Figure, his serum CPR levels gradually fell to <0.3 ng/mL on the 8th day of hospitalization. Similarly, his urinary CPR levels decreased from 59.2 μg/day on day 2 to 9.9 μg/day on day 6. We subsequently discovered that his casual CPR level had been abnormally high (11.78 ng/mL with a blood glucose level of 118 mg/dL, at four hours after breakfast) 2 weeks before his hospitalization after examining a stored blood sample. By adjusting the amount of insulin according to his blood glucose levels, ketosis was averted. The patient was discharged from hospital on the 16th day of hospitalization with a prescription of 52 units of insulin daily. After his blood glucose level was stabilized, nivolumab treatment was resumed. Tumor regression continued to be observed at 6 months after this episode. The patient provided his written informed consent for the publication of this case report.

Discussion

We encountered a patient with nivolumab-related FT1DM whose CPR levels were not depleted at the time of the initial diagnosis of hyperglycemia; moreover, his CPR level had been abnormally high 2 weeks before his hospitalization.

The type of diabetes in this case was nivolumab-related FT1DM. FT1DM is characterized by a markedly rapid onset of hyperglycemia with ketoacidosis, with near-normal HbA1c levels despite the presence of severe hyperglycemia. A negative islet-related autoantibody status, the absence of insulin-secretion capacity, even at the onset of disease, and elevated serum pancreatic enzyme levels are also noted. According to the Japanese Diabetes Society guideline (2), the following criteria are required to confirm the diagnosis of FT1DM: 1) the occurrence of diabetic ketosis or ketoacidosis soon (approximately 7 days) after the onset of hyperglycemic symptoms; 2) a plasma glucose level of ≥288 mg/dL and a glycated hemoglobin level of <8.7% (National Glycohemoglobin Standardization Program value) at first visit; 3) urinary C-peptide excretion <10 μg/day or a fasting serum C-peptide level of <0.3 ng/mL and <0.5 ng/mL after intravenous glucagon (or after meal) load at the onset of disease. Neither DKA nor the absence of insulin secretion was observed in our patient at the time of his first visit to our department; this was possibly due to the timing of the patient's examination being in the very early stage after the onset of FT1DM. His glycated albumin (GA) level (18.9%) and GA/HbA1c ratio (3.05) were relatively low in comparison to

Table 2. Specific Examinations.

Examination	Value	Unit	Examination	Value	Unit
Meal tolerance test (Day 2)			Endocrinological test		
Fasting PG	227	mg/dL	TSH	0.728	μIU/mL
2-h postprandial PG	487	mg/dL	FT3	2.3	pg/mL
Fasting CPR	2.97	ng/mL	FT4	1.6	ng/dL
2-h postprandial CPR	3.52	ng/mL	GH	0.48	ng/mL
			IGF-1	153	ng/mL
Glucagon loading test (Day 3)			LH	0.1	mIU/mL
CPR 0 min	2.64	ng/mL	FSH	7.48	mIU/mL
CPR 6 min	3.31	ng/mL	ACTH	34.9	pg/mL
			Cortisol	18.4	μg/dL
Urinary CPR			PRL	12.62	ng/mL
Day 2	59.2	μg/day	PRA	1.3	ng/mL/h
Day 6	9.9	μg/day	PAC	152	pg/mL
Pancreatic islet-associated autoantibodies			Viral antibody titers	Day 1	Day 14
Anti-GAD antibody	<5.0	U/mL	Mumps	×16	×8
Anti-IA-2 antibody	<0.4	U/mL	Coxsackie B4	×4	×8
Anti-IAA antibody	<0.4	U/mL	Coxsackie B5	×4	×4
Anti-ZnT8 antibody	<10	U/mL	EBVCA IgG	×80	×80
			EBVCA IgM	<×10	<×10
HLA-typing analysis			VZV IgM	1.27	1.93
HLA-DRB1	09:01:02 12:01:01		CMV IgG	71.8	38.4
HLA-DQB1	03:01:01 03:03:02		CMV IgM	0.54	0.56
HLA-DPB1	05:01:01		Rubella virus IgM	0.12	0.14
HLA-DQA1	03:02 05:05				

PG: plasma glucose, CPR: C-peptide immunoreactivity, GAD: glutamic acid decarboxylase, IA-2: tyrosine phosphatase-related islet antigen 2, IAA: insulin autoantibody, ZnT8: zinc transporter 8, HLA: human leukocyte antigen, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, GH: growth hormone, IGF-1, insulin-like growth factor-1, LH: luteinizing hormone, FSH: follicle stimulating hormone, ACTH: adrenocorticotropic hormone, PRL: prolactin, PRA plasma renin activity, PAC: plasma aldosterone concentration, EBVCA: Epstein-Barr virus capsid antigen, VZV: varicella zoster virus, CMV: cytomegalovirus

previously reports on patients with FT1DM (GA: 23.6± 4.3%; GA/HbA1c ratio: 3.9±0.5) (3). Given that GA reflects short-term glycemic control (i.e., approximately 14 days), the patient's FT1DM may have been diagnosed before his GA levels rose and while his insulin secretion was still preserved. As such, he would likely have been diagnosed with DKA had he visited at a later time, given that his CPR level was exhausted within 1 week of hospitalization. That the patient was negative for islet-related autoantibodies and had elevated levels of elastase 1 supported the diagnosis of FT1 DM. Additionally, his HLA type (HLA-DRB1* 09:01-HLA-DQB1* 03:03) was previously reported to be associated with acute-onset T1DM (4). After ruling out other causes, such as viral infection or drug-induced hypersensitivity syndrome, the cause of FT1DM was deemed to be nivolumab treatment (5).

Given the patient's CPR level of 5.92 ng/mL, his ability to secrete insulin appeared to be preserved at the time of his first visit, which might have caused us to overlook the onset of FT1DM. Table 3 summarizes previously published case reports on PD-1 inhibitor-related T1DM, including DKA and changes in the serum level of CPR (6-21). Most previously reported patients had depleted insulin secretion or DKA at their initial visit; 2 patients reported by Matsumura et al. and Saito et al. had preserved CPR levels without DKA (20, 21). As with our patient, their subject's insulin secretion was gradually depleted. As mentioned above, the Japanese Diabetes Society criteria for the diagnosis of FT1 DM includes the absence of insulin secretion capacity, and FT1DM may be overlooked if a patient's CPR level appears to be preserved. Clinicians should therefore consider the possibility of FT1DM if sudden hyperglycemia is detected, even if the CPR level is not depleted; DKA can be prevented with prompt insulin treatment (as was observed in the present case). Although the number of patients treated with PD-1 inhibitors is increasing, many of the clinicians who use these drugs will not be endocrinologists; as such, our patient represents an exceptional educational example of

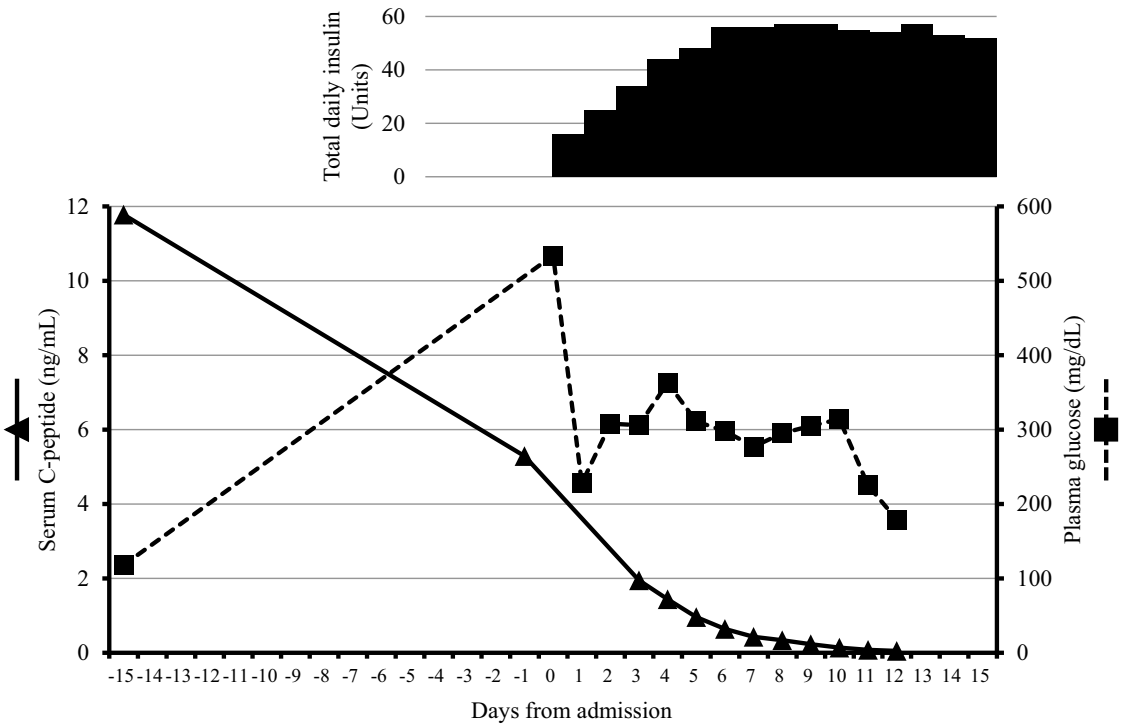

Figure. **Sequential changes of the serum C-peptide and plasma glucose levels before and after admission. The casual glucose or C-peptide levels were measured on day -15, day 0, and day 1. The fasting glucose or C-peptide levels were measured after day 2. Insulin was administered on day 0 with the dose increased daily, as shown.**

Table 3. **Summary of Reported Patients with PD-1 Inhibitor-related Type 1 Diabetes Mellitus.**

Ref.	Sex/ Age	Cancer	Anti-PD-1Ab	DKA	PG	CPR	Autoantibodies	HLA type
6	F/54	Melanoma	Pembrolizumab	(+)	n.r.	n.r.	GAD (+)	DRB1*04, DQB1*03:02
7	M/60	Melanoma	Pembrolizumab	(+)	27 mmol/L (486 mg/dL)	57 pmol/L (0.17 ng/mL)	GAD (-), IA-2(-)	n.r.
8	F/55	Melanoma	Nivolumab	Ketonuria	580 mg/dL	1.0 ng/mL	Negative	DRB1*04:05, DQB1*04:01
9	M/76	NSCLC	Pembrolizumab	(-)	40 mmol/L (721 mg/dL)	0.81 ng/mL	GAD (+), IA-2 (+)	n.r.
10	M/51	RCC	Nivolumab	(+)	763 mg/dL	Undetectable	GAD (-), IA-2 (-)	n.r.
11	F/34	NSCLC	Nivolumab	(+)	739 mg/dL	<0.1 ng/mL	GAD (+), IA-2 (+)	A30:01,30:02 DR9
12	M/31	NSCLC	Nivolumab	(+)	n.r.	<0.03 ng/mL	GAD (+)	DRB1*04:05, DQB1*04:01
12	F/62	NSCLC	Nivolumab	Ketonuria	246 mg/dL	n.r.	GAD (-)	DRB1*09:01 DQB1*03:03
13	F/73	NSCLC	Nivolumab	(+)	>1,000 mg/dL	0.06 ng/mL	GAD (+)	DR3-DQ2, DR4-DQ8
14	M/73	NSCLC	Nivolumab	(-)	708 mg/dL	0.97 ng/mL	Negative	DRB1*09:01, DQB1*03:03, DRB1*01:01, DQB1*05:01
15	M/73	Melanoma	Nivolumab	(+)	500 mg/dL	Undetectable	GAD (+), IA-2(+), ZnT8 (+)	n.r.
16	M/42	Melanoma	Nivolumab	(+)	728 mg/dL	n.r.	Negative	n.r.
17	F/74	NSCLC	Nivolumab	(+)	1,060 mg/dL	0.2 ng/mL	GAD (+)	n.r.
18	F/68	RCC	Nivolumab	(-)	473 mg/dL	Undetectable	Negative	DRB1*09:01, DQB1*03:03
19	F/63	Melanoma	Nivolumab	(+)	661 mg/dL	0.08 ng/mL	n.r.	DRB1*09:01
20	M/68	NSCLC	Nivolumab	(-)	330 mg/dL	3.16 ng/mL	Negative	A*24:02, DRB1*09:01, DRB1*15:02
21	M/82	NSCLC	Pembrolizumab	(-)	319 mg/dL	2.03 ng/mL	Negative	DRB1* 12:01
Our patient	M/77	RCC	Nivolumab	(-)	379 mg/dL	5.92 ng/mL	Negative	DRB1* 09:01:02 12:01:01, DQB1* 03:01:01 03:03:02, DPB1* 05:01:01, DQA1 *03:02 05:05

PD-1: programed death-1, DKA: diabetic ketoacidosis, PG: plasma glucose, CPR: C-peptide immunoreactivity, HLA: human leukocyte antigen, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma, GAD: glutamic acid decarboxylase, IA-2: tyrosine phosphatase-related islet antigen 2, ZnT8: zinc transporter 8, n.r.: not reported

PD-1 inhibitor-related T1DM.

By examining a stored blood sample, we found that our patient's casual CPR level was abnormally high (11.78 ng/mL) 2 weeks before his hospitalization. Few patients have exhibited transient hyperinsulinemia and hypoglycemia before the onset of T1DM (22). As the etiology of nivolumab-related FT1DM is thought to be the invasion of PD-1-positive T cells into islet cells (23), hyperinsulinemia likely occurred as a result of pancreatic islet cell destruction. To the best of our knowledge, ours is the first patient reported to exhibit hyperinsulinemia before the onset of PD-1 inhibitor-related FT1DM. Our patient's course suggests that the destruction of pancreatic islet cells by nivolumab was already occurring 2 weeks before the detection of hyperglycemia. Although our patient did not experience hypoglycemia, our findings suggest that clinicians should consider the possibility of FT1DM when sudden hypoglycemia or hyperglycemia are detected, because the former may occur as a result of hyperinsulinemia due to the destruction of pancreatic islet cells.

Recently, the Japan Diabetes Society reported the characteristics and clinical course of anti-PD-1 antibody-related T1 DM (24). According to this report, the insulin secretion capacity of most patients was exhausted at about 2-3 weeks after the onset of disease, which is slower than in patients with fulminant type 1 diabetes but faster than in patients with acute-onset type 1 diabetes. Our patient also had this characteristic. Because anti-PD-1 antibody-related T1DM varies from typical FT1DM to acute-onset T1DM, the authors proposed that it would be appropriate to consider anti-PD-1 antibody-related T1DM a distinct entity and to introduce a newly coined name for this entity (24). Thus, our case also would be classified as a new type of T1DM in the future.

In conclusion, we encountered a patient with nivolumab-related FT1DM in whom we observed a gradual change of serum CPR levels. Clinicians should not rule out the possibility of FT1DM in nivolumab-treated patients when detecting sudden hyperglycemia, even if the CPR level is not depleted.

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

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