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Fulminant Type 1 Diabetes Mellitus Developed about Half a Year after Discontinuation of Immune Checkpoint Inhibitor Combination Therapy with Nivolumab and Ipilimumab: A Case Report

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The cytotoxic T-lymphocyte antigen-4 and programmed cell death 1 pathways are novel therapeutic targets in immune checkpoint inhibitor (ICI) therapy for cancer. However, they may cause endocrine-related adverse events, including hypophysitis, autoimmune thyroiditis and type 1 diabetes mellitus (DM). Moreover, delayed immune-related adverse events (irAEs) after discontinuation of ICI therapy have been reported. Here we report a 60-year-old female patient with advanced renal cell carcinoma with brain metastasis who was treated with nivolumab, ipilimumab and prednisolone. At the 3rd course of combination therapy, the administration was discontinued due to the onset of colitis and the dosage of prednisolone was increased. About half a year after discontinuation, she was admitted to the hospital with general malaise, hyperglycemia (330 mg/dL) and diabetic ketoacidosis. Glycated hemoglobin level was 6.5%. Islet-related autoantibodies were negative. The glucagon tolerance test showed complete depletion of insulin. Therefore, we diagnosed fulminant type 1 DM and treated with multiple daily injections of insulin. The onset of type 1 DM was rapid in many cases treated with combination therapy of ICIs. The present case is a rare case in which fulminant type 1 DM developed about half a year after discontinuation of nivolumab and ipilimumab. The literature shows two cases of type 1 DM occurring 4 months after discontinuation of ICI therapy by nivolumab or atezolizumab. The present case indicates that regular monitoring is mandatory for fulminant type 1 DM and other delayed irAEs after discontinuation of ICI therapy even under the low-dose prednisolone treatment.

Keywords: diabetic ketoacidosis; fulminant type 1 diabetes mellitus; immune checkpoint inhibitor; ipilimumab; nivolumab
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Introduction

Immune checkpoint inhibitors (ICIs) have an anticancer effect by removing a negative regulatory signal for T-cell activation from the microenvironment. They include antibodies against cytotoxic T-cell-associated antigen (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand-1 (PD-L1). Two of them are nivolumab (anti-PD-1 monoclonal antibody) and ipilimumab (anti-CTLA-4 monoclonal antibody). These ICIs are sometimes associated with endocrine-related adverse events, including hypophysitis, thyroiditis, and type 1 diabetes mellitus (DM) (Corsello et al. 2013; Ryder et al. 2014; Hughes et al. 2015; Martin-Liberal et al. 2015; Sakurai et al 2018). Hypophysitis and thyroiditis are the most common endocrine-related adverse events, whereas type 1 DM is rare. Fulminant type 1 DM is characterized by rapid-onset diabetic ketoacidosis, low glycated hemo-

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globin A1c (HbA1c) value, undetectable serum C-peptide and negative islet-related autoantibodies (Imagawa et al. 2000).

Couey et al. (2019) performed a PubMed literature review from 2008 through 2018 and revealed delayed immune-related adverse events (irAEs) manifesting ≥ 90 days after discontinuation of immunotherapy. The target organ system most abundantly involved in delayed irAEs was the endocrine system, such as adrenal (adrenal insufficiency) and thyroid (hypothyroidism). Moreover, two cases of type 1 DM occurring 4 months after discontinuation of ICI therapy by nivolumab or atezolizumab have recently been reported by the Japanese groups (Nishioki et al. 2020; Mae et al. 2021).

Here we report an additional patient with advanced renal cell carcinoma (RCC) who developed fulminant type 1 DM about half a year after discontinuation of nivolumab and ipilimumab.

Case Presentation

A 60-year-old woman without DM was diagnosed with left RCC and brain metastasis. She had bronchial asthma and no family history of autoimmune disease and DM. She was treated with nivolumab (3 mg/kg every 3 weeks) and ipilimumab (1 mg/kg every 3 weeks), and treated with prednisolone (10 mg/day) for preventing cerebral edema. After third course of nivolumab and ipilimumab, she underwent left nephrectomy (Day 72 from the first day of nivolumab and ipilimumab administration). After nephrectomy, nivolumab and ipilimumab therapy was discontinued due to acute colitis induced by nivolumab and ipilimumab therapy, and the dosage of prednisolone was increased to 40 mg/day to treat colitis, followed by a tapered dose of prednisolone (Fig. 1). DM had not developed at this time (Fig. 1).

About seven months (216 days) after the first administration and about half a year (174 days) after the last administration, she was admitted to the hospital with general malaise, hyperglycemia, metabolic acidosis and presence of ketones bodies in urine (Day 216) (Table 1). In spite of marked hyperglycemia, HbA1c was relatively low (6.5%) (Table 1). Blood levels of β-hydroxybutyrate (8,150 μmol/L; reference range < 85 μmol/L) and acetoacetic acid (1,830 μmol/L; reference range < 55 μmol/L) were elevated (Table 1). Anti-glutamic acid decarboxylase was negative (Table 1). Human leukocyte antigen (HLA) typing showed haplotype DRB1*11:01:01, DRB1*12:01:01 and DQB1*03:01:01, which were not those associated with autoimmune or fulminant type 1 DM. Serum C-peptide levels were decreased and the glucagon tolerance test showed complete depletion of insulin (Day 219) (Table 1). Therefore, we diagnosed fulminant type 1 DM induced by nivolumab and ipilimumab therapy. There was no increase in amylase, lipase and elastase 1, and computed tomogra-

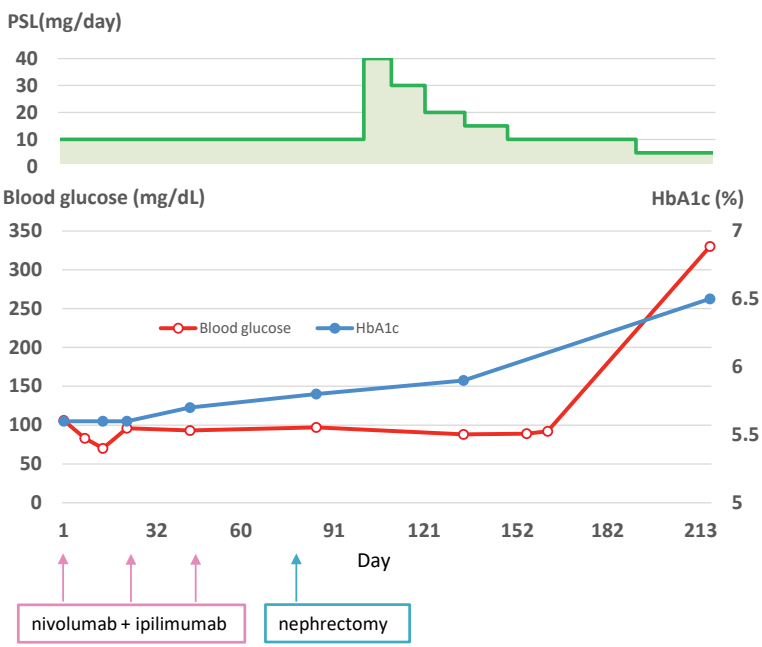

Fig. 1. Clinical course of the patient.
Treatment and laboratory data are shown. The first day at which nivolumab and ipilimumab were administered was defined as Day 1. Prednisolone (PSL; 10 mg/day) was administered to prevent cerebral edema. At Day 101, the dosage of PSL was increased to 40 mg/day to treat colitis, followed by a tapered dose of PSL. The days of the combination therapy of nivolumab and ipilimumab are indicated by arrows. The day of left nephrectomy is shown by an arrow. Blood glucose levels (open circle) and glycated hemoglobin (HbA1c: closed circle) were normal during nivolumab and ipilimumab combination therapy. However, about seven months after the first administration and about half a year after the last administration, hyperglycemia was observed, whereas HbA1c was relatively low (Day 216).
PSL, prednisolone.

Table 1. Laboratory data results 216 days (Day 216) after the first administration of nivolumab and ipilimumab glucagon stimulation test (Day 219).

		(Reference values)
Glucose	330 mg/dL	
HbA1c	6.5%	(4.6-6.1)
Urinary ketone	4+	
Amylase	33 IU/L	(37-120)
Lipase	47 IU/L	(6-48)
Elastase 1	125 ng/dL	(0-300)
Acetoacetic acid	1,830 μmol/L	(< 55)
3-OHBA	8,150 μmol/L	(< 85)
TSH	2.130 μIU/mL	(0.5-5.0)
FT3	1.75 pg/mL	(2.3-4.0)
FT4	1.39 ng/dL	(0.9-1.7)
Serum C-peptide	0.25 ng/mL	(0.8-2.5)
Urinary C-peptide	2.2 μg/day	(29.2-167)
GAD antibody	< 5.0	(< 5.0)
Arterial blood gases		
pH	7.226	(7.35-7.45)
pCO_2	23.7 mmHg	(32-48)
pO_2	118 mmHg	(83-108)
HCO_3^-	9.5 mmol/L	(21-28)
Anion gap	12.8 mmol/L	(7.0-16.0)
Glucagon stimulation test		
C-peptide (0 min)	0.08 ng/mL	
C-peptide (6 min)	0.08 ng/mL	
ΔC-peptide	0 ng/mL	
HLA typing	DRB1 11:01:01 12:01:01	
	DQB1 03:01:01	

HCO_3^-, bicarbonate ion; 3-OHBA, 3-hydroxybutyric acid; TSH, thyroid stimulating hormone; FT3, triiodothyronine; FT4, free thyroxine; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen.

phy showed no complication of pancreatitis (data not shown). Multiple daily injections of insulin were started (8 units/day). Nivolumab and ipilimumab therapy remained discontinued, and DM remained insulin-dependent.

Informed consent was obtained from the subject on this case report.

Discussion

We report a case of advanced RCC treated with nivolumab and ipilimumab combination therapy, resulting in delayed immune-related fulminant type 1 DM. ICIs were discontinued due to adverse effect, but fulminant type 1 DM developed about half a year (174 days) after discontinuation. There were no other endocrine-related adverse events during the course. Genetic predisposition associated with the development of fulminant type 1 DM has been identified (Tsutsumi et al. 2012), but was not present in this case.

The occurrence frequency of ICI-induced type 1 DM is lower than that of other endocrine-related adverse events, with nivolumab at about 0.1-0.2% and anti-CTLA-4 monotherapy being extremely rare (Ishikawa et al. 2017; de Filette et al. 2019). The cases with ICI-induced type 1 DM on ipilimumab were received anti-PD-1 or interferon pretreatment. There is not much information available on occurrence of type 1 DM with nivolumab and ipilimumab combination therapy. However, it is characterized by the relatively earlier onset compared to the therapy using a single agent (Zezza et al. 2019). On average, combination therapy-induced DM was diagnosed after 2.7 cycles, although anti PD-1 or PD-L1 monotherapy is after 4.5 cycles (de Filette et al. 2019). The presence or absence of islet autoantibodies can also affect the time to onset of ICI-induced type 1 DM. Akturk et al. reported that the time to onset is significantly more rapid in islet-related autoantibodies-positive cases (Akturk et al. 2019).

There have been cases of ICI-induced type 1 DM that developed half a year after the start of ICI administration

Table 2. Clinical and laboratory data on delayed immune-related type 1 diabetes mellitus (T1DM) in case reports.

	The present case	Nishioki et al. (2020)	Mae et al. (2021)
Age/Sex	60/F	73/F	59/M
Cancer	RCC	Recurrent NSCLC	Gastric cancer
ICI regimen	Nivolumab and ipilimumab	Atezolizumab	Nivolumab
Cycles of ICI therapy	3 cycles	2 cycles	12 cycles
Period from the last ICI administration to the onset of T1DM	About six months	Four months	Four months
Prior glucocorticoid administration	Yes	No	No
Plasma glucose (mg/dL)	330	962	690
HbA1c (%)	6.5	7.3	10.6
Blood ketone bodies	+	+	N/A
Urine ketone bodies	+	−	+
T1DM-related autoantibodies	− (GAD)	− (GAD, IA-2)	− (GAD, IA-2, ZnT8)

T1DM, type 1 diabetes mellitus; F, female; M, male; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; ZnT8, zinc transporter 8.

(Baden et al. 2018), but these cases have developed during treatment with ICI. Table 2 summarizes clinical and laboratory data on delayed immune-related type 1 DM after discontinuation of ICI therapy in recently reported 2 cases (Nishioki et al. 2020; Mae et al. 2021) and the present case. Both single ICI and a combination of two ICIs caused delayed immune-related type 1 DM. All three cases showed negative type 1 DM-related autoantibodies, such as anti-glutamic acid decarboxylase antibody.

It has been suggested that ICIs have long-lasting effects. Osa et al. (2018) reported nivolumab binds to T cells for more than 20 weeks, and the therapeutic effect may persist for at least 20 weeks after discontinuation of nivolumab. Moreover, in the present case, low-dose glucocorticoids were administered to treat colitis and prevent cerebral edema. Glucocorticoids have the effect of suppressing the function of T cell, and may differentially affect the immune system depending on the dose. Tokunaga et al. (2019) reported that both low-dose and high-dose glucocorticoids inhibit the differentiation of low-affinity CD8+T cell into memory T cell. Therefore, in the present case, low-dose glucocorticoid might weaken the efficacy of ICIs and inhibit the differentiation of low-affinity CD8+T cell. These effects of low-dose glucocorticoid might maintain a long-term effect of ICIs, and resulted in delayed irAE of fulminant type 1 DM.

ICI-induced type 1 DM has a low incidence, but is a life-threatening adverse effect if the detection and treatment are delayed. Since regular monitoring is performed during ICI administration, early detection is possible, but there are cases such as this case that develop after a certain period of time. In conclusion, regular monitoring must be mandatory for delayed irAEs, particularly fulminant type 1 DM during at least half a year after discontinuation of ICI administration.

Conflict of Interest

The authors declare no conflict of interest.

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