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CASE REPORT

Two cases with fulminant type 1 diabetes that developed long after cessation of immune checkpoint inhibitor treatment

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ABSTRACT

Various immune-related adverse events (irAEs), including fulminant type 1 diabetes (FT1D), are known to be associated with immune checkpoint inhibitors (ICIs). We experienced two lung adenocarcinoma cases who developed fulminant type 1 diabetes long after discontinuation of ICI therapies. One, a 74-year-old male, received nivolumab and developed fulminant type 1 diabetes 44 days after the last infusion. The other, an 85-year-old male, received atezolizumab and developed fulminant type 1 diabetes 171 days after the last infusion. Clinical ICI treatment guidelines recommend laboratory tests during ICI treatments but the necessity of tests in patients whose ICI therapy has been discontinued is not clearly described. These cases indicate that blood glucose monitoring should be continued at least for several months, and that patients should be informed of the possibility of fulminant type 1 diabetes after ICI discontinuation, because fulminant type 1 diabetes progresses rapidly and can be life-threatening if not promptly recognized.

INTRODUCTION

While immune checkpoint inhibitors (ICIs), such as anti-programmed cell death 1 (PD-1), anti-PD-ligand 1 (PD-L1), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-antibodies, are effective for treating numerous malignancies, several immune-related adverse events (irAEs)[1], such as thyroid dysfunction, pneumonitis, colitis, cutaneous toxicities, have been reported. Type 1 diabetes (T1D), especially fulminant type 1 diabetes (FT1D), is also reportedly associated with ICI treatments[2]. Because fulminant type 1 diabetes results from acute and near-total destruction of pancreatic β cells, it can be life-threatening if unrecognized[3]. Therefore, it is important to detect its onset. Clinical ICI treatment guidelines generally recommend repeated laboratory tests, including the measurement of blood glucose levels during the treatment period[4–6]. However, the necessity of monitoring glucose levels in patients in whom the ICI therapy had been terminated is not clearly described in most guidelines. One of the guidelines notes that another measurement 4–6 weeks after the last cycle of immunotherapy may be necessary[7].

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We experienced two cases who developed fulminant type 1 diabetes more than 6 weeks after their last ICI treatments. In particular, one developed fulminant type 1 diabetes approximately 6 months after the last ICI infusion.

CASE PRESENTATION 1

A 74-year-old male with no history of diabetes was diagnosed as having lung adenocarcinoma with metastases in the liver, bone, and brain. He received first-line chemotherapy with gefitinib for 6 months, but with little therapeutic response. Thereafter, second-line chemotherapy with nivolumab every 2 weeks was started. Before the first infusion of nivolumab, the postprandial plasma glucose was 103 mg/dL, glycated hemoglobin (HbA1c) was 6.1%, the postprandial serum C-peptide immunoreactivity (CPR) level was 2.1 ng/mL. Computed tomography demonstrated an abnormal pericardial effusion and growth of the primary tumor. Since malignant pericarditis had worsened, nivolumab administration was terminated after its sixth cycle.

Six weeks after the last infusion of nivolumab, he became aware of thirst, polydipsia, and polyuria. His weight decreased by 3.7 kg. Laboratory data on day 44 after ICI cessation

revealed marked hyperglycemia and ketonuria and he was transferred to our hospital as an emergency.

While his postprandial plasma glucose was elevated to 507 mg/dL, HbA1c was 7.1%. Fasting serum C-peptides were below the lower limit of detection. He had ketonuria with markedly elevated 3-hydroxybutylate and acetoacetate in the blood (Table 1). Autoantibodies to glutamic acid decarboxylase (GAD) and insulinoma-associated antigen-2 (IA-2) were both negative. We diagnosed fulminant type 1 diabetes with diabetic ketosis, and suspected nivolumab to be associated with its development. Ketosis showed a prompt improvement and his blood glucose was well controlled on intensive insulin therapy. Human leukocyte antigen (HLA) typing identified no specific alleles known to be related to type 1 diabetes (Table 1).

CASE PRESENTATION 2

An 85-year-old male with no history of diabetes was diagnosed as having lung adenocarcinoma with carcinomatous pleurisy. He was started on a treatment regimen with carboplatin, pemetrexed, and atezolizumab every 3 weeks. Before the first infusion of atezolizumab, the fasting plasma glucose and HbA1c were 86 mg/dL and 5.7%, respectively. After the sixth cycle, this treatment was stopped because of a renal function decline. On day 171 after the last infusion of atezolizumab, he complained of appetite loss and thirst. Four days later, the postprandial plasma glucose was 735 mg/dL and he had lost 1.4 kg. He was transferred to our hospital.

Although his postprandial plasma glucose was 705 mg/dL, HbA1c was 7.4%. Fasting serum C-peptide was beneath the lower limit of detection. He had ketonuria and the blood levels of both 3-hydroxybutylate and acetoacetate were increased (Table 2). Autoantibodies to GAD and IA-2 were both negative. The glucagon loading test showed no increase in CPR levels (Table 2), indicating complete β cell loss.

Based on these findings, we diagnosed fulminant type 1 diabetes and suspected atezolizumab to be involved in its development. He had type 1 diabetes-susceptible HLA types, i.e., DRB1*09:01-DQB1*03:03. He initially received continuous insulin infusion intravenously. Thereafter, he was managed with basal-bolus insulin therapy.

DISCUSSION

In both of our cases, the criteria for diagnosing fulminant type 1 diabetes, established by the committee of the Japanese Diabetes Society[8], were all met. Related findings, including undetectable islet-related autoantibodies and a diabetes duration of less than 1 week before the start of insulin treatment were also met in these two cases. Therefore, both patients were diagnosed as having fulminant type 1 diabetes. Of course, we cannot rule out the possibility that the fulminant type 1 diabetes development in these two patients was unrelated to their ICI treatments. However, neither patient exhibited symptoms suggesting viral infection, a known trigger of fulminant type 1 diabetes[8], just prior to its onset. In addition, pharmacodynamics reportedly indicated a sustained high occupancy of PD-1 on circulating T cells of more than 2 months following nivolumab infusion[9]. Thus, ICIs were deemed to be the most likely cause of their fulminant type 1 diabetes development.

Most cases who developed ICI-associated irAEs were reported during the period of ICI treatment, while several irAEs, such as pneumonitis, hepatitis, colitis, and cutaneous toxicities, were reported to have developed despite ICI treatments having already been discontinued[10]. Clinical ICI treatment guidelines recommend repeated laboratory tests, including the measurement of blood glucose levels, during the treatment period. In many guidelines, however, a concrete description is lacking of how long these laboratory tests should be continued after treatment cessation. The guidelines promulgated by the European Society for Medical Oncology note that another measurement 4–6 weeks after the last cycle of immunotherapy may be necessary[7]. However, our two patients developed fulminant type 1 diabetes more than 6 weeks after receiving their last ICI

Table 1 | Laboratory results of case 1

Biochemistry		TSH	0.439 μIU/mL	**Arterial blood gas analysis**	
T-Bil	0.8 mg/dL	FT4	1.1 ng/dL	pH	7.369
γ-GTP	33 U/L	FT3	1.25 pg/mL	PCO_2	39.8 mmHg
AST	23 U/L	Lipase	26 U/L	HCO_3^-	22.4 mmol/L
ALT	25 U/L	Amylase	57 U/L	Base Excess	−2.1 mmol/L
LDH	161 U/L	Elastase 1	326 ng/dL	**Diabetes-related data**	
BUN	26 mg/dL	Acetoacetate	1,144 {mol/L	HbA1c	7.1%
Cre	0.69 mg/dL	3-Hydroxybutyric acid	1,894 {mol/L	GA	29%
UA	5.8 mg/dL	Total ketone bodies	3,038 {mol/L	FPG	227 mg/dL
TP	6.8 g/dL	**Complete blood count**		Serum CPR	<0.01 ng/mL
Alb	3.4 g/dL	WBC	4,600 {L	Anti-GAD antibody	<5.0 U/mL
Na	137 mmol/L	Hb	11.9 g/dL	Anti-IA-2 antibody	<0.6 U/mL
K	3.6 mmol/L	Plt	160 × 10^3 {L	**HLA typing (day 11)**	
Cl	98 mmol/L	**Urinalysis**		HLA-A31, A01	
Ca	9 mg/dL	Protein	±	HLA-B54, B39	
P	3.5 mg/dL	Glucose	4+	HLA-DRB1 *13:02	
CRP	0.89 mg/dL	Ketone body	2+	HLA-DQB1 *06:04	

Table 2 | Laboratory results of case 2

Biochemistry		Lipase	29 U/L	**Diabetes-related data**	
T-Bil	0.6 mg/dL	Amylase	124 U/L	HbA1c	7.4%
γ-GTP	35 U/L	Elastase 1	180 ng/dL	GA	29%
AST	18 U/L	Acetoacetate	729 μmol/L	FPG	223 mg/dL
ALT	12 U/L	3-Hydroxybutyric acid	2,688 μmol/L	Serum CPR	<0.01 ng/mL
LDH	227 U/L	Total ketone bodies	3,417 μmol/L	Anti-GAD antibody	<5.0 U/mL
BUN	34 mg/dL	**Complete blood count**		Anti-IA-2 antibody	<0.6 U/mL
Cre	1.54 mg/dL	WBC	6,100/μL	Urinary CPR (day 8)	0.61 μg/day
UA	7.1 mg/dL	Hb	11.4 g/dL	**Glucagon loading test (day 13)**	
TP	7.3 g/dL	Plt	167 × 10^3/μL	CPR 0 min	<0.01 ng/mL
Alb	3.4 g/dL	**Urinalysis**		CPR 6 min	<0.01 ng/mL
Na	138 mmol/L	Protein	-	**HLA typing (day 12)**	
K	4.1 mmol/L	Glucose	4+	HLA-A24:02, 31:01	
Cl	96 mmol/L	Ketone body	1+	HLA-B35:01, 44:03	
Ca	9.1 mg/dL	**Arterial blood gas analysis**		HLA-DRB1*09:01, 13:02	
CRP	2.19 mg/dL	pH	7.406	HLA-DQB1*03:03, 06:04	
TSH	2.72 μIU/mL	PCO_2	38.3 mmHg		
FT4	1.59 ng/dL	HCO_3^-	23.5 mmol/L		
FT3	1.58 pg/mL	Base excess	−0.4 mmol/L		

treatments. In the second case, especially, approximately 6 months had passed since the last infusion of atezolizumab.

These cases are very informative for both physicians and patients. Monitoring blood glucose even after stopping ICIs should continue for several months, or even longer, to detect the development of fulminant type 1 diabetes. In addition, we need to inform patients who have undergone ICI therapies that they must urgently present to a hospital if they develop symptoms of acute-onset diabetes and ketoacidosis, such as polyuria, polydipsia, weight loss, vomiting, and digestive disorders, even long after the cessation of ICI therapies. We physicians should keep in mind that ICI administrations can induce type 1 diabetes even several months after the discontinuation of these therapies.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: We informed the patient or patient's family of the case report, and they gave their consent.
Approval date of registry and the registration No. of the study/-trial: October19, 2021, No. 23579.
Animal studies: N/A.

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