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Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes

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Programmed cell death-1 (PD-1), an immunoreceptor, is located on T cells and pro-B cells and interacts with its ligands to inhibit T cell activation and proliferation, thereby promoting immunological self-tolerance. Nivolumab, an anti-PD1 antibody, blocks PD-1 and can restore anticancer immune responses by abrogating PD-1 pathway-mediated T-cell inhibition. Autoimmune adverse events are expected with PD-1 therapy. Fulminant type 1 diabetes is the subtype of type 1 diabetes. The clinical feature is the extremely rapid progression of hyperglycemia and ketoacidosis. Here we describe a 66-year-old woman with advanced melanoma who was treated with nivolumab. After 4 months and six doses of the medicine, the patient was admitted to the hospital with complaints of nausea and vomiting. The laboratory data showed ketonuria, hyperglycemia (531 mg/dl), high anion gap metabolic acidosis, HbA1c (7.3%), and absence of insulin-secreting capacity. These data are compatible with the criteria of fulminant type 1 diabetes. The patient was diagnosed with diabetic ketoacidosis because of fulminant type 1 diabetes. The findings of this case indicated that nivolumab can cause fulminant type 1 diabetes. Diabetic ketoacidosis due to fulminant type 1 diabetes is potentially fatal condition. Thus, diabetic ketoacidosis due to fulminant type 1 diabetes should be considered in the differential diagnosis when patients treated with nivolumab complain of gastrointestinal symptoms.

Keywords: autoimmune diseases; diabetic ketoacidosis; fulminant type 1 diabetes; nivolumab; programmed cell death-1
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Introduction

Nivolumab, a fully human IgG4 anti-programmed cell death-1 (PD-1) antibody, blocks PD-1 and can restore anti-cancer immune responses by abrogating PD-1 pathway-mediated T-cell inhibition (Adachi and Tamada 2015). It is also known as one of the immune-checkpoint inhibitors. Autoimmune side effects are expected in immune-checkpoint-blockade therapy (Pardoll 2012).

Fulminant type 1 diabetes (FD) is a subtype of ketosis-onset type 1 diabetes characterized by rapid disease progression within several days or few weeks and almost complete insulin deficiency. The criteria for a definite diagnosis of FD include markedly rapid onset of hyperglycemia with ketoacidosis, near normal glycated hemoglobin (HbA1c) levels despite remarkable hyperglycemia, and an absence of insulin-secreting capacity, even at disease onset (Imagawa et al. 2012). FD, if disregarded or not diagnosed, directly results in the death of the patient. When the diagnosis of fulminant type 1 diabetes is made or strongly suspected, treatment of the patient must be started immediately, as in all other cases of type 1 diabetes. Otherwise, the disease will rapidly deteriorate, leading to the death of the patient, generally within 24 h (Hanafusa and Imagawa 2007). Hence, an early diagnosis of FD is important.

In this report, we describe a case of FD in a patient receiving nivolumab therapy.

Case Presentation

A 66-year-old female without any history or family history of diabetes presented with irregular vaginal bleeding. A tumor of approximately 4 cm in the vagina underwent local resection. Pathological diagnosis was melanoma. The margin of resection was positive, and vaginal and cervical metastasis was detected. As adjuvant therapy, nivolumab was administered at a dose of 2 mg/kg every 3 weeks. After three doses, she presented with diarrhea and weight loss. However, nivolumab was continued because of an improvement in the vaginal melanoma. Four days prior to admission, she developed anorexia; 121 days after starting nivolumab and after a total of six doses, she presented at the emergency room complaining of nausea, vom-

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Table 1. Laboratory Data on Admission.

Variable		Reference range	Variable		Reference range
Glucose	531 mg/dL		Total ketone body	3716μmol/L	< 130
HbA1c	7.3%	4.6-6.2	Acetoacetic acid	1134μmol/L	< 55
Urinary ketone	+++		3-OHBA	2582μmol/L	< 95
pH	7.294	7.35-7.45	TSH	2.05 μ IU/mL	0.4-4.7
pCO_2	25.8 mmHg	37.0-44.0	FT4	1.28 ng/dL	1.0-1.8
pO_2	99.2 mmHg	80-100	TR Ab	negative	
HCO_3^-	12.2 mEq/L	22-26	TPO Ab	negative	
Anion gap	23.8 mEq/L	10-14	Serum-C-peptide	0.23 ng/mL	0.8-2.3
Creatinine	0.81 mg/dL	0.31-1.1	Urinary-C-peptide	< 0.9 μ g/day	29.2-167
Amylase	43 IU/L	37-125	GAD antibody	negative	
Lipase	74 U/L	11-53	IA-2 antibody	negative	
Na	127 mEq/L	135-147	ZnT8 antibody	negative	
K	6.0 mEq/L	3.3-4.8			
Cl	91 mEq/L	98-108			
Δ C-peptide (6min)during Glucagon stimulation test	0.01 ng/mL	>1.0	HLA typing	DRB1 11:01 13:02:01 DQB1 03:01:01 06:04:01	

HCO_3^-, bicarbonate ion; 3-OHBA, 3-hydroxybutyric acid; TSH, thyroid stimulating hormone; FT4, free tetraiodothyronine; TR Ab, TSH receptor antibody; TPO Ab, anti-thyroid peroxides antibody; GAD, Glutamic Acid Decarboxylase; IA-2, Insuslinoma-associated Antigen-2; ZnT8, Zinc transporter 8.

iting, and anorexia.

There were no upper respiratory inflammation symptoms, thirst, polyuria, or abdominal pain. On physical examination, the patient's blood pressure was 114/83 mmHg, her pulse rate was 75 beats/min, and her body temperature was 36.1°C. Her height and weight were 163 cm and 34 kg, respectively. The patient was alert, and there was no abdominal tenderness. The remaining findings of the neurological and general examinations were unremarkable. There was no sign of pancreatitis as evidenced by ultrasonography and magnetic resonance imaging. Data on laboratory tests are shown in Table 1. Ketonuria, hyperglycemia, and high anion gap metabolic acidosis were found, and the patient was diagnosed with diabetic ketoacidosis (DKA). She initially received isotonic saline and continuous insulin infusion (12 units per day). On the third hospital day, upon resolution of DKA, she was switched from continuous insulin infusion to multiple daily injections of insulin. At discharge, her insulin regimen was 6 units as basal and 29 units as bolus.

A glucagon stimulation test revealed severely impaired insulin secretion. Tests for various islet-related autoantibodies were negative. These findings along with a HbA1c of < 8.7% and the clinical course were compatible with the criteria of FD. We diagnosed the patient with FD, and nivolumab administration was continued (two doses). To date, her diabetes is controlled with basal-bolus insulin therapy.

Informed consent

The patient provided written informed consent for her clinical data to be published in a medical journal.

Discussion

Two important clinical issues are highlighted in this study. First, nivolumab has a potential to induce FD. Second, gastrointestinal symptoms due to DKA observed during nivolumab administration should be distinguished from gastrointestinal adverse events due to nivolumab.

Nivolumab, a PD-1 inhibitor, has been reported to cause type 1 diabetes (Martin-Liberal et al. 2015). The incidence of type 1 diabetes was increased in PD-1 blocked NOD mouse (Wang et al. 2005; Kochupurakkal et al. 2014). Moreover, low PD-1 expression in peripheral CD4+ T cells in type 1 diabetes has been reported (Fujisawa et al. 2015). Inhibiting the PD-1 pathway may cause type 1 diabetes. Therefore, nivolumab, an anti-PD-1 antibody, may cause type 1 diabetes. A few reports indicated that PD-1 inhibitors may indeed cause type 1 diabetes (Gaudy et al. 2015; Hughes et al. 2015; Martin-Liberal et al. 2015). In the 8 reported cases, three met the criteria for FD including low HbA1c, absence of islet-related autoantibodies, and undetectable serum C-peptide. Therefore, we diagnosed our case with nivolumab-induced FD.

When gastrointestinal symptoms develop during nivolumab therapy, it is important to distinguish between DKA due to FD and pure gastrointestinal adverse events due to nivolumab, such as diarrhea, nausea, vomiting, or

stomachache. DKA due to FD is potentially fatal if the diagnosis and treatment are delayed. The most frequent adverse events in nivolumab therapy are fatigue, rash, pruritus, nausea, diarrhea and hepatitis. Nausea and vomiting have been observed in 8.4%-37% and 4.7%-20% of patients undergoing nivolumab therapy, respectively (Topalian et al. 2014; Weber et al. 2015; Robert et al. 2015). Gastrointestinal symptoms, such as nausea and vomiting, are also more frequently observed in FD than in acute type1 diabetes at disease onset. Diarrhea and nausea/vomiting have been observed in 5.5% and 64.5% patients with FD, respectively (Imagawa et al. 2003). Thus, nausea and vomiting reflect symptoms that are shared among adverse events of nivolumab and FD at disease onset. Differential diagnosis of gastrointestinal symptoms is very important in nivolumab therapy. Plasma glucose and blood gas analyses should be carried out upon the presentation of these gastrointestinal symptoms with a view to testing for FD in patients who are being treated with nivolumab.

The female sex, the type of cancer (melanoma), and a past history of autoimmune thyroiditis were shared features in three cases of nivolumab-induced FD (Gaudy et al. 2015). Our case, however, did not have any past history of autoimmune thyroiditis, and a history of thyroid disease may not be a consistent clinical feature in nivolumab-induced FD. The interval between the start of nivolumab and the development of FD ranged from < one month to five months in the literatures and in our case. An association between FD and HLA DRB1*04:05-DQB1*04:01 has been reported (Imagawa et al. 2012). Our case, however, did not exhibit this HLA type. The clinical features of nivolumab-induced FD remain incompletely characterized, and further accumulation of cases is required to elucidate the mechanism of nivolumab-induced FD.

Nivolumab was initially approved for the treatment of advanced malignant melanoma in 2014 and then for non-small cell lung cancer in 2015. The number of patients receiving nivolumab treatment is expected to increase; hence, the incidence of nivolumab-induced FD may also increase.

In conclusion, nivolumab, an anti-PD-1 antibody, therapy can induce FD. Gastrointestinal symptoms observed during and after nivolumab treatment may be due to the adverse events of nivolumab and could possibly be DKA due to FD. The gastrointestinal adverse events of nivolmab are common and are palliatively treated; however, fulminant diabetes is a life-threatening complication if the treatment is delayed or the patient could not be treated. Hence, careful consideration of the differential diagnosis is critical in nivolumab-treated patients who present with gastrointestinal symptoms.

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Conflict of Interest

The authors declare no conflict of interest.

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