

Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy

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ABSTRACT

Anti-programmed cell death-1 (PD-1) antibodies are regarded as a risk factor for insulin-dependent diabetes mellitus as a side-effect. While a small number of cases have been reported, evidence remains limited. This is the first report of an Asian patient developing insulin-dependent diabetes during anti-PD-1 therapy. A 55-year-old euglycemic woman receiving nivolumab for malignant melanoma showed abrupt onset of ketonuria, and elevated levels of plasma glucose (580 mg/dL) and hemoglobin A1c (7.0%). Over the next 2 weeks, serum C-peptide levels fell below the limit of detection. Islet autoantibodies were negative, and the patient showed a human leukocyte antigen haplotype associated with type 1 diabetes. Anti-PD-1 therapy can cause rapid onset of insulin-dependent diabetes, possibly because of inappropriate activation of T cells. Human leukocyte antigen haplotypes might be related to the onset of this disease. Physicians should be aware of this serious adverse event and carry out routine blood glucose testing during anti-PD-1 therapy.

INTRODUCTION

Programmed cell death-1 (PD-1) is expressed on T cells, B cells and macrophages, and negatively regulates immune responses by binding to PD-1 ligands (PD-L1 or PD-L2). Most cancers escape from the host immune system as a result of the presence of those ligands. Nivolumab is a monoclonal antibody against the PD-1 receptor, achieving disinhibition of tumor-specific immune responses¹. Although such immune checkpoint inhibitors have been shown to be highly useful against several types of cancer, descriptions of endocrinological adverse events have been accumulating. Some reports have described new-onset diabetes after anti-PD-1 pharmacotherapy^{2–5}, but the evidence remains limited. We describe herein the case of a woman who developed fulminant type 1 diabetes during anti-PD-1 therapy, with some important findings that should contribute to elucidation of the pathogenesis.

CASE REPORT

A 55-year-old Japanese woman receiving nivolumab (2 mg/kg, once every 3 weeks) for malignant melanoma was referred to the Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University Hospital, Oita, Japan, as a result of hyperglycemia. She had no history of

diabetes and no evidence of pancreatic metastases. She had been receiving nivolumab without combination with anti-T lymphocyte-associated antigen 4 antibody for 12 months at the time of referral, after 1 year of chemotherapy with dacarbazine, nimustine, cisplatin and tamoxifen. Blood glucose levels had been normal until the last blood examination, which was carried out 3 weeks before her referral. Although marked

Table 1 | Laboratory results of the patient

	Results
Glucagon (pg/mL)	134 (70–174)
Amylase (U/L)	36 (37–125)
Elastase1 (ng/dL)	93 (<300)
Lipase (IU/L)	31 (11–53)
Thyroid-stimulating hormone receptor antibody (IU/L)	<1.0 (<2.0)
Thyroglobulin antibody (IU/mL)	10.9 (<28)
Thyroid peroxidase antibody (IU/mL)	5.9 (<16)
Antipituitary antibody	(–)
Antinuclear antibody	(–)
Time-series data of serum CPR (ng/mL)	(0.61–2.09)
Day 0	1.0
Day 2	0.7
Day 7	0.3
Day 17	<0.1

Normal ranges given in parentheses where appropriate. CPR, C-peptide.

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Table 2 | Summary of previous reports

Case no.	Literature	Age/sex (ethnicity)	Primary diagnosis	Pertinent history	Anti-PD-1 drug	Other chemotoxins	Preceding viral infection	Diabetes presentation	CPR and glucose	Time after anti-PD-1	Islet cell autoantibodies	HLA
1	Okamoto <i>et al.</i>	55 F (Japanese)	Malignant melanoma	Dyslipidemia gastric ulcer	Nivolumab	Dacarbazine, nimustine, cisplatin, tamoxifen	(-)	Ketonia 580 mg/dL HbA1c 7.0%	1.0 ng/dL and 580 mg/dL	12 months	GAD (-) ICA (-) IA-2 (-) ZnT8 (-)	DRB1*04:05, DQB1*04:01
2	Hughes <i>et al.</i> ⁴	55 F (Not listed)	Malignant melanoma	Autoimmune thyroid disease	Nivolumab	Ipilimumab, prednisone	Not listed	DKA 532 mg/dL HbA1c 6.9%	<0.1 ng/dL and 52 mg/dL	5 months	None	A2.1+, DR4+
3	Hughes <i>et al.</i> ⁴	83 F (Not listed)	Non-small-cell lung cancer	Remote smoker	Nivolumab	None	Not listed	DKA 350 mg/dL HbA1c 7.7%	<0.1 ng/dL and 336 mg/dL	<1 month	GAD (+)	A2.1+, DR4+
4	Hughes <i>et al.</i> ⁴	63 M (Not listed)	Renal cell carcinoma	Hypertension	Nivolumab	Proleukin, bevacizumab, interferon	Not listed	Random glucose 247 mg/dL HbA1c 8.2%	1.3 ng/dL and 79 mg/dL	4 months	GAD (+) ICA (+) IAA (+)	A2.1+, DR4+
5	Hughes <i>et al.</i> ⁴	58 M (Not listed)	Small-cell lung cancer	Type 2 diabetes mellitus	Nivolumab	Carboplatin/etoposide, paclitaxel	Not listed	DKA 749 mg/dL HbA1c 9.7%	<0.1 ng/dL and 284 mg/dL	1 week	GAD (+)	A2.1+
6	Hughes <i>et al.</i> ⁴	64 F (Not listed)	Malignant melanoma	Autoimmune thyroid disease psoriasis	Pembrolizumab	None	Not listed	Ketonia 703 mg/dL HbA1c 7.4%	0.5 ng/dL and 268 mg/dL	<1 month	None	DR4+
7	Martin-Liberal <i>et al.</i> ³	54 F (Not listed)	Malignant melanoma	Asthma	Pembrolizumab	Ipilimumab	Not listed	DKA BS, HbA1c: not shown	Not listed	6 weeks (after three infusions)	GAD (+) ICA (-) IAA (-)	DRB1*04, DOB1*03:02 (HLA A2 DR4 DQ8)
8	Mellati <i>et al.</i> ²	70 M (Not listed)	Adenocarcinoma of the lung	Not listed	(Anti-PD-L1 Ab)	Not listed	Not listed	DKA 411 mg/dL HbA1c 9.8%	0.3 ng/dL and 411 mg/dL	15 weeks	GAD (-) IAA (-)	Not listed
9	Mellati <i>et al.</i> ²	66 F (Not listed)	Sarcomatoid squamous cell carcinoma of the jaw	Not listed	Anti-PD-1 Ab	Not listed	Not listed	DKA 752 mg/dL HbA1c 9.4%	<0.1 ng/dL and 752 mg/dL	7 weeks	GAD (+) ICA (-) IAA (-) ZnT8 (-)	DR3-DQ2/DR4-DR8
10	Gaudy <i>et al.</i> ⁵	44 F (Caucasian)	Malignant melanoma	Autoimmune thyroid disease	Pembrolizumab	Ipilimumab	(-)	DKA 908 mg/dL HbA1c 6.85%	Undetectable	5 weeks	GAD (-) ICA (-)	Not listed

Ab, antibodies; CPR, C-peptide; DKA, diabetic ketoacidosis; F, female; GAD, glutamic acid decarboxylase; HbA1c, hemoglobin A1c; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen-2; IAA, insulin autoantibody; ICA, islet cell antibody; M, male; PD-1, programmed cell death ligand-1; PD-L1, programmed cell death ligand-1; ZnT8, zinc transporter 8.

hyperglycemia (580 mg/dL) and ketonuria had been noted at the first visit to our department, hemoglobin A1c level was relatively low (7.0%), suggesting rapid onset. The short period from onset to ketosis, extreme hyperglycemia and relatively low hemoglobin A1c level suggested fulminant type 1 diabetes⁶. Findings at onset, such as serum C-peptide level (1.0 ng/mL) and urinary C-peptide excretion (12.6 µg/day), did not meet the diagnostic criteria for fulminant type 1 diabetes, but serum C-peptide levels dropped to below the limit of detection over the next 2 weeks, and glucagon tolerance testing showed complete depletion of insulin. As treatment for fulminant type 1 diabetes, multiple daily injections of insulin were started. Negative results were obtained for all islet autoantibodies (glutamic acid decarboxylase, insulinoma-associated antigen-2, insulin autoantibodies and zinc transporter 8), and further investigation revealed the DRB1*04:05-DQB1*04:01 human leukocyte antigen (HLA) haplotype, which is strongly associated with autoimmune type 1 diabetes in Japan⁷. No blood examination findings or symptoms suggested acute viral infection before onset, and pancreatic enzyme levels at onset were not elevated (Table 1). Computed tomography showed mild atrophy of the pancreas, and endoscopic ultrasonography showed several findings generally seen in early chronic pancreatitis, namely hyperechoic foci and strands, lobularity, and cysts. Although those findings are often seen among individuals with heavy intake of alcohol, the patient had no history of drinking. Nivolumab treatment was resumed 1 month after the patient's referral, and no further side-effects have been observed to date. Islet autoantibodies have remained negative, and insulin secretion has remained depleted as of 3 months after onset. Treatment with multiple insulin injections is ongoing.

DISCUSSION

The present report described a case of new-onset diabetes with anti-PD-1 therapy that showed a rapid fall into insulin-dependence. Onset was considered to be associated with the pharmacotherapy, as no other potential factors or causes (e.g., family history, irregular lifestyle, viral infection, pancreatic metastasis of the cancer or drugs other than nivolumab) could be identified. Our search of the literature found four reports (8 cases) of onset or worsening of diabetes in association with anti-PD-1 therapies (not limited to nivolumab), and all except one of those cases presented with diabetic ketoacidosis or ketonuria followed shortly thereafter by insulin-dependence^{2–5}. Considering the rapid onset, severity and potential mortality of those situations, routine measurement of both hemoglobin A1c and blood glucose levels is warranted after starting administration of anti-PD-1 antibodies. In the present case, we might have observed the very early stage of fulminant type 1 diabetes, considering that the patient was not completely insulin-dependent for the first few days after onset.

In the present case, all results for islet autoantibodies were negative. Half of the previously reported patients who developed insulin-dependent diabetes after anti-PD-1 therapy

likewise showed no detectable autoantibodies (Table 2). The pathogenesis in these patients thus seems to differ at least partly from that of conventional autoimmune type 1 diabetes involving islet autoantibodies. Ansari *et al.*⁸ found no correlation between insulin autoantibody levels and development of diabetes with blockade of the PD-1–PD-L1 pathway in mice, and some mice developed diabetes despite the apparent absence of autoantibodies.

In contrast, reduced activity of PD-1 is apparently common to both conventional autoimmune type 1 diabetes and anti-PD-1 therapy-related diabetes. Fujisawa *et al.*⁹ recently showed a reduction in PD-1 expression on T cells in type 1 diabetes compared with other types of diabetes. Perri *et al.*¹⁰ also suggested that lower expression of PD-1 on T cells causes inappropriate activation of those cells in insulin-dependent diabetes. Anti-PD-1 drugs could produce a similar situation, and PD-1 reduction might cause inappropriate activation of T cells resulting in autoimmune responses against pancreatic β-cells.

Human leukocyte antigen typing in this case showed haplotype DRB1*04:05-DQB1*04:01, which is the haplotype most closely associated with autoimmune or fulminant type 1 diabetes in Japan⁷. Reported cases to date have also shown high-risk HLA genotypes for autoimmune diabetes (Table 2). Considering these findings, HLA could be involved in the onset of insulin-dependent diabetes with anti-PD-1 therapy. Autoimmune diabetes might develop when anti-PD-1 drugs are given to at-risk patients, through imbalanced activation and inhibition of T cells, although the underlying mechanisms remain unclear. Biomarkers predictive of anti-PD-1 therapy-related diabetes have yet to be clarified, but HLA haplotypes could be one such biomarker. Further accumulation of cases and evidence is required.

Anti-PD-1 therapy can cause insulin-dependent diabetes that develops and progresses rapidly in a manner differing from conventional autoimmune diabetes, possibly through inappropriate activation of T cells. These cases might not present with autoantibodies to islet cells. HLA haplotypes might be related to disease onset. Physicians should be aware of this serious adverse event, and carry out routine blood testing during anti-PD-1 therapy. Further studies are required to elucidate the pathogenesis and background factors for this form of diabetes.

DISCLOSURE

The authors declare no conflict of interest.

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