Case of fulminant type 1 diabetes induced by the anti-programmed death-ligand 1 antibody, avelumab

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Keywords
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ABSTRACT
With the expansive use of immune checkpoint inhibitors, the frequency of immune-related adverse events, including autoimmune type 1 diabetes, has been exponentially increased. The anti-programmed death-ligand 1 antibody, avelumab, has recently been approved for metastatic Merkel cell carcinoma therapy. Here, we report a patient that developed fulminant type 1 diabetes during avelumab treatment. An 81-year-old woman with no history of diabetes received avelumab for metastatic Merkel cell carcinoma. Elevated plasma glucose level (483 mg/dL), hemoglobin A1c level (7.5%) and ketosis were observed after 10 courses of avelumab without any symptoms related to hyperglycemia. As the laboratory tests showed insulin depletion, we diagnosed her with fulminant type 1 diabetes induced by avelumab. This is the first reported case of avelumab-induced type 1 diabetes, illustrating the necessity for close monitoring of glycemic control during avelumab therapy, as well as other immune checkpoint inhibitors.

INTRODUCTION
Immune checkpoint inhibitors (ICIs), including anti-programmed death-1 (PD-1) antibodies and cytotoxic T-lymphocyte-associated protein 4 antibodies, have been expansively used for cancer treatment. However, increased frequency of immune-related adverse events, including type 1 diabetes, has been well recognized. Type 1 diabetes as a result of immune-related adverse events has been reported to be 1.0–3.0% in ICI monotherapy with nivolumab and <1.0% in ICI monotherapy with pembrolizumab.

The US Food and Drug Administration approved the anti-programmed death-ligand 1 (PD-L1) immunoglobulin G1 antibody, avelumab, as a treatment for metastatic Merkel cell carcinoma (MCC) in 2017. MCC is a very rare skin cancer with a high mortality rate of ≥15%. Surgery and radiation therapy can control localized MCC as high as 95% for the first-line treatment; however, more than half of the MCC cases relapse with extremely low response rates to chemotherapy¹. Avelumab was expected to be the second-line treatment for metastatic MCC. With limited use of avelumab, there are insufficient data on type 1 diabetes due to avelumab. Here, we report a patient that developed fulminant type 1 diabetes during avelumab treatment.

CASE REPORT
In 2016, a 79-year-old woman was diagnosed with stage IIIIB MCC, and underwent surgery and radiation therapy at the Department of Plastic Surgery at Hokkaido University Hospital in Sapporo, Japan. Two years after the first treatment, she was found to have retroperitoneal metastasis, and ICI monotherapy with avelumab was started in February 2018. Before avelumab, her plasma glucose and hemoglobin A1c levels were 110 mg/dL and 6.1%, respectively. She received avelumab monotherapy (523 mg every 2 weeks) for 5 months (10 times in total) without any symptoms or any laboratory findings of hyperglycemia.

At a regular visit in July 2018, elevated plasma glucose level (483 mg/dL) and hemoglobin A1c level (7.5%) were detected without any hyperglycemia symptoms or any signs of antecedent infection. The patient was referred and admitted to the Internal Medicine II, Hokkaido University Hospital on the same day of the visit. Her height, bodyweight and body mass index were 147 cm, 48.7 kg and 22.5 kg/m², respectively. Venous blood gas analysis showed no metabolic acidosis, but blood ketone bodies...
were increased (Table 1). A glucagon loading test, carried out 1 week after the admission, and 24-h urinary C-peptide immunoreactivity showed severe insulin deficiency. Neither antiglutamic acid decarboxylase antibodies nor anti-islet antigen 2 antibodies were positive (Table 1). No metastasis signature in the pancreas was detected with computed tomography. Based on her clinical course and laboratory findings, we diagnosed the patient with fulminant type 1 diabetes mellitus induced by avelumab. Human leukocyte antigen (HLA) analysis showed she had DRB1*09:01:02, DRB1*14:54:01, DQA1*01:04, DQA1*03:02, DQB1*05:02:01 and DQB1*03:03:02, being partially concordant with type 1 diabetes susceptible haplotype. Post-avelumab, positron emission tomography–computed tomography showed the disappearance of the retroperitoneal metastasis. Although avelumab administration was suspended because of the ICI-induced fulminant type 1 diabetes mellitus, it will be resumed with intensive insulin therapy if any sign of MCC recurrence appears. The patient’s hemoglobin A1c levels were between 7.4 and 8.2% after discharge with intensive insulin therapy.

We obtained informed consent and received a consent form from this patient.

**DISCUSSION**

To the best of our knowledge, this is the first report of a patient with fulminant type 1 diabetes mellitus induced by ICI monotherapy with avelumab. A case with fulminant type 1 diabetes mellitus due to anti-PD-L1 antibody, atezolizumab, and cases with type 1 diabetes due to anti-PD-L1 antibody, atezolizumab or durvalumab, have been reported. The patients with fulminant type 1 diabetes mellitus due to atezolizumab developed diabetic ketoacidosis. These reports showed that ICI-induced type 1 diabetes can be induced by anti-PD-L1 antibody, as well as anti-PD-1 and anti-CLTA-4 antibodies. According to the phase II clinical trial of avelumab, two out of 1,738 (0.1%) patients developed type 1 diabetes. This percentage was lower than that observed with anti-PD-1 antibodies, possibly because of the limited therapeutic application of avelumab.

It has been discussed that ICI-induced type 1 diabetes is caused by the destruction of pancreatic β-cells by autoreactive T cells. A substantial reduction in PD-1 expression in CD4+ T cells has been observed in patients with type 1 diabetes, and this suppression might activate autoreactive T cells. As avelumab is a human anti-PD-L1 immunoglobulin G1 antibody that specifically inhibits PD-L1/PD-1 interactions, ICI-induced type 1 diabetes due to avelumab might have a similar pathogenesis to anti-PD-1 antibodies. Colli et al. reported PD-L1 expression in pancreatic β-cells from type 1 diabetes patients, but not from non-diabetic individuals, suggesting indirect mechanisms of anti-PD-L1 antibody to cause β-cell destruction other than the local PD-1/PD-L1 pathway.

Certain HLA haplotypes with an increased risk of type 1 diabetes and fulminant type 1 diabetes mellitus have been...
reported; these HLA types are associated with an increased risk of the onset of ICI-induced type 1 diabetes. In the case described here, HLA typing was not concordant with these peculiar HLA haplotypes. To verify the genetic risk of developing ICI-induced type 1 diabetes, analysis of single-nucleotide polymorphism has been started.

In the clinical guidelines for the management of ICI therapy, the need for monitoring glucose levels is emphasized. Measuring blood glucose levels is recommended at baseline and at each treatment cycle during the induction for 12 weeks. Thereafter, it is suggested that this measurement be carried out every 3–6 weeks. The Japan Diabetes Society recommends measuring blood glucose levels on every visit for ICI-treated patients. The patient in the present report was found to be hyperglycemic at a regular visit without any symptoms. ICIs lead to rapid destruction of pancreatic β-cells, ultimately to diabetic ketoacidosis. From the national survey of type 1 diabetes related to anti-PD-1 antibody in Japan, 50.0% (11/22) of the patients met the criteria for fulminant type 1 diabetes mellitus and 38.9% (7/18) of the patients developed diabetic ketoacidosis. The present case showed the need for close monitoring of glycemic control during avelumab therapy, as well as the other kinds of ICIs.

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DISCLOSURE
The authors declare no conflict of interest.

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