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LETTER TO THE EDITOR

Intrinsic insulin secretion capacity might be preserved by discontinuing anti-programmed cell death protein 1 antibody treatment in 'anti-programmed cell death protein 1 antibody-induced' fulminant type 1 diabetes

Fulminant type 1 diabetes has been described as a subtype of type 1 diabetes characterized by accelerated progression and without the presence of islet-associated autoantibody. Thus far, several reports have documented the occurrence of type 1 diabetes, including the fulminant type, after anti-programmed cell death protein 1 (PD-1) antibody treatment for malignant tumors[1]. T cells are deactivated by inhibitory signals, such as those produced by PD-1 and the ligand PD-L1[2], and PD-1 inhibition by anti-PD-1 antibody probably triggers an autoimmune phenomenon through the reduction of the immune checkpoint function of T cells.

Previously, we reported a case of fulminant type 1 diabetes that developed after the treatment of a malignant melanoma with the anti-PD-1 antibody, nivolumab[3]. A 63-year-old Japanese woman with melanoma received eight courses of anti-PD-1 immunotherapy, which was discontinued 6 weeks before the onset of fulminant type 1 diabetes. Laboratory data at the onset of fulminant diabetes were as follows: plasma glucose 661 mg/dL, pH 6.95, total ketone body 8,477.5 μmol/L, glycated hemoglobin 8.6%, serum C-peptide 0.08 ng/mL, elastase 1 1100 ng/dL and CRP 1.89 mg/dL. We recently evaluated the human leukocyte antigen type in this patient and found that she had an *HLA-DRB1*09:01* genotype, which is a susceptible human leukocyte antigen type in Japanese type 1 diabetes patients.

Although previous reports have documented similar cases[1,2], we believe no report has described the changes in intrinsic insulin secretion capacity; that is, C-peptide level, after the onset of fulminant type 1 diabetes caused by anti-PD-1 antibody treatment.

The present patient was followed up without using anti-PD-1 antibody after the onset of fulminant type 1 diabetes, because the treatment was ineffective against malignant melanoma.

As shown in the Figure 1, the serum C-peptide level was relatively higher (range 0.12–0.37 ng/mL) than that seen in typical fulminant type 1 diabetes[4]. Furthermore, even 10 months after the onset, C-peptide was still detected (0.17 ng/mL). During this time-course, the patient's glycated hemoglobin ranged 7.0–8.6%, postprandial plasma glucose level 145–348 mg/dL and insulin dose 46–48 units/day.

A reason for the residual β-cell function in the present case might be the effect of intensive insulin therapy, especially at the onset of fulminant type

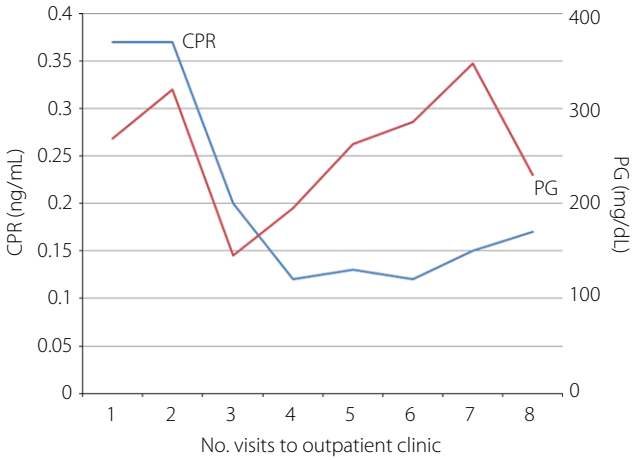

Figure 1 | Changes in the C-peptide (CPR) and plasma glucose (PG) level after the onset of fulminant type 1 diabetes in the present case. C-peptide levels were examined in postprandial condition. The *x*-axis shows the number of visits to our outpatient clinic (Saitama Medical University, Moroyama, Saitama, Japan) (duration of visit interval: 4–6 weeks).

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1 diabetes. Nevertheless, we suspect that not only the intensive insulin therapy, but also the discontinuation of anti-PD-1 antibody treatment, might have prevented the β-cell destruction after the onset of fulminant type 1 diabetes caused by anti-PD-1 antibody treatment.

If the prognosis will be worsened by the discontinuation of the anti-PD-1 antibody treatment, we might have to continue the treatment throughout the patient's life. However, if there is an alternative treatment choice for the malignancy, the discontinuation of anti-PD-1 antibody treatment might be the one of choice, because this could help preserve pancreatic β-cell function in the patient.

We should monitor changes in the intrinsic insulin secretion capacity; that is, C-peptide level, of patients with 'anti-PD-1 antibody-induced' fulminant type 1 diabetes, and discuss whether treatment discontinuation can be considered by accumulating and analyzing reports of similar cases henceforth.

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