

Nivolumab-induced fulminant type 1 diabetes with precipitous fall in C-peptide level

Anti-programmed cell death protein 1 (PD-1) antibodies activate the immune system to attack tumors and are used as anticancer agents. However, anti-PD-1 antibody therapy is reported to induce serious side-effects, including type 1 diabetes mellitus¹. We describe here a case of anti-PD-1 antibody therapy, nivolumab-induced type 1 diabetes mellitus, which developed within 9 days of treatment. A 79-year-old man with negative history of diabetes started treatment with nivolumab for non-small cell lung cancer. Plasma glucose level (PG) monitoring three times daily for 7 days showed fluctuation of PG from 106 to 180 mg/dL (Figure 1). On day 8, pre-dinner PG increased to 340 mg/dL, necessitating treatment with an insulin sliding scale. On day 9, the pre-lunch PG further increased to 630 mg/dL. Physical examination and abdominal ultrasonography were negative. Blood tests showed normal glycosylated hemoglobin level (6.1%) and high pancreatic enzyme levels (amylase 238 IU/L, lipase 490 IU/L). Blood and urine tests confirmed lack of ketone bodies and metabolic acidosis. Serum C-peptide level (CPR) was <0.03 ng/mL and anti-glutamic acid decarboxylase antibody (GADA) was negative. Based on these findings, the diagnosis was fulminant type 1 diabetes mellitus. Human leukocyte antigen deoxyribonucleic acid genetic typing showed DRB1*09:01-DQB1*03:03 haplotype. There was no evidence of preceding acute viral infection (based on lack of clinical features and negative tests for viruses). Anti-thyroglobulin antibody test was

positive, but thyroid function tests were normal.

The immediate management included extracellular fluid replacement and intravenous insulin. The latter was switched to multiple daily injections after restarting meals. PG was later stabilized by four units of insulin lispro before breakfast, six before lunch and four before dinner, together with four units of insulin degludec before bed, and the patient was discharged subsequently. At both 1 month and 1 year after discharge, the blood CPR was still <0.03 ng/mL. Importantly, fasting venous blood sampling on the early morning of day 8 (i.e., before onset of diabetes), showed PG of 81 mg/dL and CPR 1.56 ng/mL, suggesting endogenous insulin secretion just before the onset.

A review of similar Japanese cases showed a mean time to onset of nivolumab-associated type 1 diabetes mellitus of 155 days¹. Recently, Saito *et al.*² documented the serial changes in CPR in patients with fulminant type 1 diabetes mellitus that developed after anti-PD-1 therapy, and showed that such therapy resulted in a steady fall in CPR to <0.01 ng/mL within 16 days. Thus, it seems that the clinical course of nivolumab-associated type 1 diabetes mellitus is slower than typical fulminant type 1 diabetes mellitus (depletion within approximately 7 days). However, in the present patient, CPR fell rapidly within a single day. Thus, it seems that the effect of nivolumab on the induction of type 1 diabetes mellitus varies among individuals, stressing the need for a thorough evaluation of the effects of these compounds on type 1 diabetes mellitus in a larger number of patients.

In this regard, it is important to monitor PG frequently after the initiation of

nivolumab treatment. Similar to the present case, four patients who underwent anti-PD-1 therapy (three on nivolumab, one case on pembrolizumab) were reported to develop fulminant type 1 diabetes mellitus after the first injection³. In all four patients, fulminant type 1 diabetes mellitus developed within 20 days after a single injection. Interestingly, all four patients were positive for GADA (1,760 U/mL to >50,000 U/mL). Previous articles suggested that nivolumab-induced type 1 diabetes mellitus shows a faster clinical course in GADA-positive patients compared with negative patients, suggesting that the presence of GADA might be a useful predictor of poor clinical course of nivolumab-induced type 1 diabetes mellitus. However, in the present patient, the onset occurred very early after only a single injection despite the fact that the patient tested negative for GADA, which is a significant difference from the previous reports of nivolumab-induced type 1 diabetes mellitus. GADA were measured twice in the present patient, at the onset and at least 1 year after the onset, and the antibodies were negative on both occasions. Although other islet-associated autoantibodies, such as the islet antigen-2 antibody, were not measured at the onset, we confirmed later that islet antigen-2 antibodies were also negative at 1 year and beyond.

Administration of anti-PD-1 antibody is associated with thyroid dysfunction¹. The present patient was positive for anti-thyroglobulin antibodies. In Japan, autoimmune thyroiditis frequently occurs as an autoimmune complication with type 1 diabetes mellitus, and previous reports suggest the involvement of a common human leukocyte antigen haplotype⁴. Thus, the development of nivolumab-associated type 1 diabetes mellitus seems to involve more than one factor.

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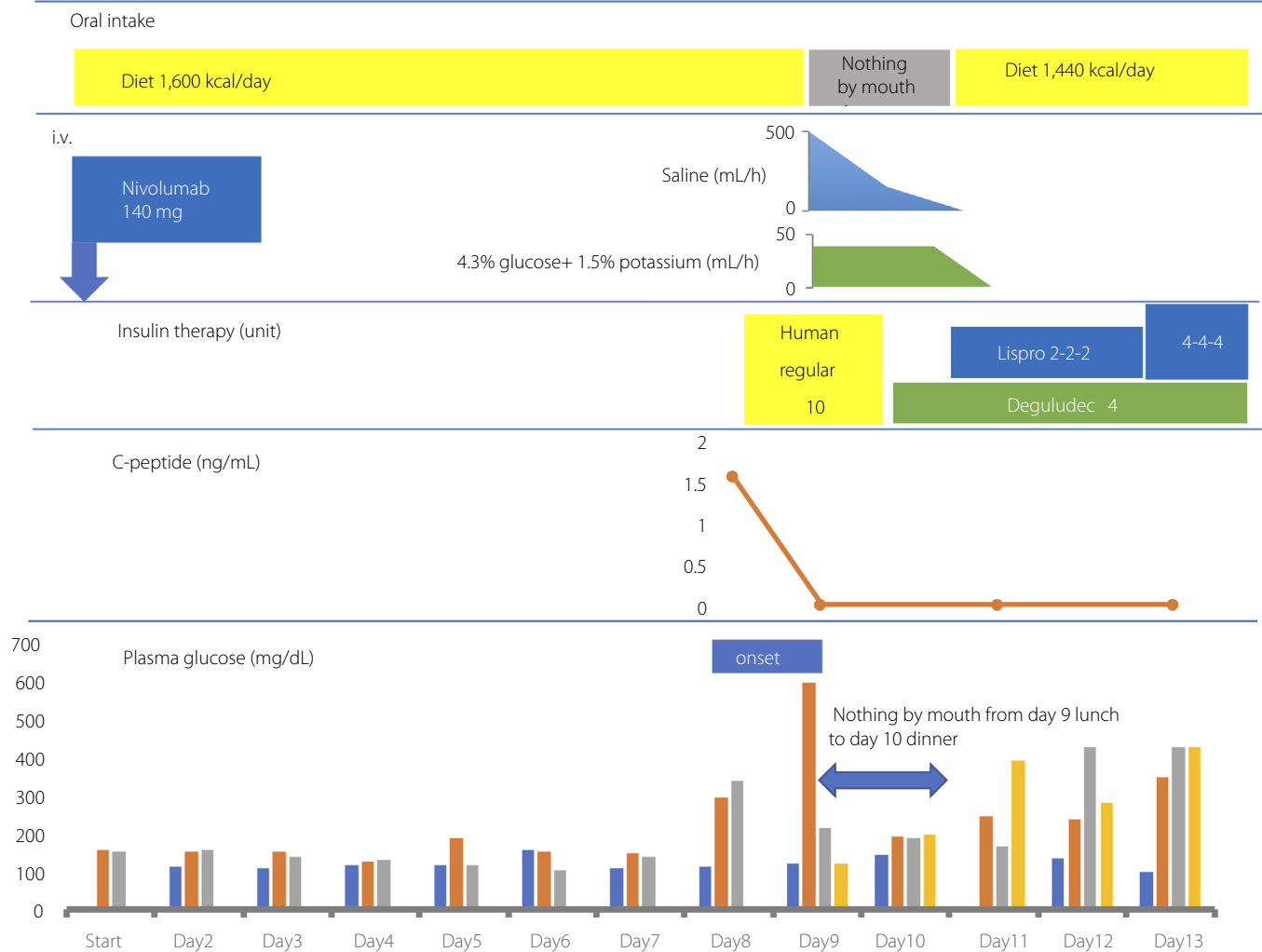


Figure 1 | Daily changes in plasma glucose and serum C-peptide levels after initiation of treatment of nivolumab. i.v., intravenous fluid.

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DISCLOSURE

The authors declare no conflict of interest.

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