Detailed Time Course of Decline in Serum C-Peptide Levels in Anti–Programmed Cell Death-1 Therapy–Induced Fulminant Type 1 Diabetes

Daigo Saito, Yoichi Oikawa, Yuya Yano, Yuichi Ikegami, Atsushi Satomura, Masashi Isshiki, Susumu Kurihara, Ikuo Inoue, Mitsuhiko Noda, and Akira Shimada

Diabetes Care 2019;42:e40–e41 | https://doi.org/10.2337/dc18-1673

Fulminant type 1 diabetes (FT1D) is a novel subtype of type 1 diabetes (T1D) and is characterized by a relatively low glycated hemoglobin (HbA_{1c}) level at onset, despite the abrupt occurrence of marked hyperglycemia with ketosis or ketoacidosis (1). Recent studies have shown that anti–programmed cell death (PD)-1/anti–PD-ligand 1 (PD-L1) therapy for malignancies leads to the development of T1D including FT1D (2–4). In typical FT1D, insulin secretion capacity is completely exhausted within ~7 days after the onset (1); in some cases, a rapid loss of insulin secretion was observed during 2 days prior to onset of diabetic ketoacidosis (DKA) (5). Meanwhile, the detailed time course of insulin secretion capacity in anti–PD-1 therapy–induced FT1D has not yet been reported.

We present a case of an 82-year-old Japanese man with squamous cell cancer of the lung, who had received multiple courses of anti–PD-1 immunotherapy (pembrolizumab) every 3 weeks for ~12 months. Written informed consent was obtained from the participant. On the day of the 16th course of anti–PD-1 therapy, his casual plasma glucose and HbA_{1c} levels were 106 mg/dL and 5.8% (40 mmol/mol), respectively. However, a blood test performed on the scheduled day of the 17th course revealed his casual plasma glucose was 432 mg/dL; thus, he was immediately hospitalized without the planned course.

His height was 158.5 cm; weight, 47.0 kg; and BMI, 18.7 kg/m^2. He had no history of glucose intolerance, no evidence of preceding acute viral infection, and no hyperglycemic symptoms before and during hospitalization. The initial laboratory examination revealed the following: negative urine ketones, casual plasma glucose level 319 mg/dL, HbA_{1c} level 6.1% (43 mmol/mol), casual serum C-peptide level 2.03 ng/mL, serum creatinine level 0.76 mg/dL, normal levels of serum exocrine pancreatic enzymes, negative islet-associated autoantibodies, arterial pH level 7.404, arterial HCO_3^- level 22.7 mmol/L, and serum total ketone body level 304.5 (normal range: ≤130) μmol/L. He carried a homozygote of HLA-DRB1*12:01 allele, which is not associated with autoimmune T1D. An abdominal ultrasonography revealed the absence of swelling in the pancreas. He had no diabetes complications. Intensive insulin therapy was started immediately after admission, and his plasma glucose levels finally improved with 10 units of insulin glargine and 11, 4, and 5 units of insulin aspart before breakfast, lunch, and dinner, respectively.

During hospitalization, fasting and casual serum C-peptide levels rapidly decreased as the days progressed without obvious hypoglycemia, and insulin secretion capacity was completely exhausted in 16 days, presumably not via reduced blood glucose stimuli but via β-cell damage (Fig. 1*A* and *B*), suggesting that the pace of reduction in serum C-peptide levels was milder than that in persons with typical FT1D. However, if each serum C-peptide level had been measured under adequate glycemic control, the time course might have shown a different pattern; this is a limitation of this study. After discharge, the patient's serum C-peptide level remained below 0.01 ng/mL.

According to previous reports, the positivity rate of islet-associated autoantibodies may be relatively lower in Japanese individuals with checkpoint inhibitor–induced diabetes than in Caucasian individuals (4.76% vs. 56%, respectively) (3,6), which is consistent with the negative test results for islet-associated autoantibodies in this case. Moreover, a previous study has shown that anti-GAD antibodies (GADA)-positive T1D may develop in a shorter period of time after the initiation of anti–PD-1/anti–PD-L1 therapy than GADA-negative T1D (6). In this case, T1D developed over a long period of time (54 weeks) after the initiation of anti–PD-1 therapy, which potentially explains the negative test results for islet-associated autoantibodies.

Considering that anti–PD-1 therapy targets T-cell immunoregulatory molecules, a cellular immunity against islet-associated autoantigens may be involved in the development of T1D. However, any cellular immune responses against insulin molecules, including the main epitope of T cells in human T1D, could not be verified in this case. On this

Department of Endocrinology and Diabetes, School of Medicine, Saitama Medical University, Saitama, Japan

Corresponding author: Yoichi Oikawa, yoikawa5724@asahinet.jp

Received 6 August 2018 and accepted 18 December 2018

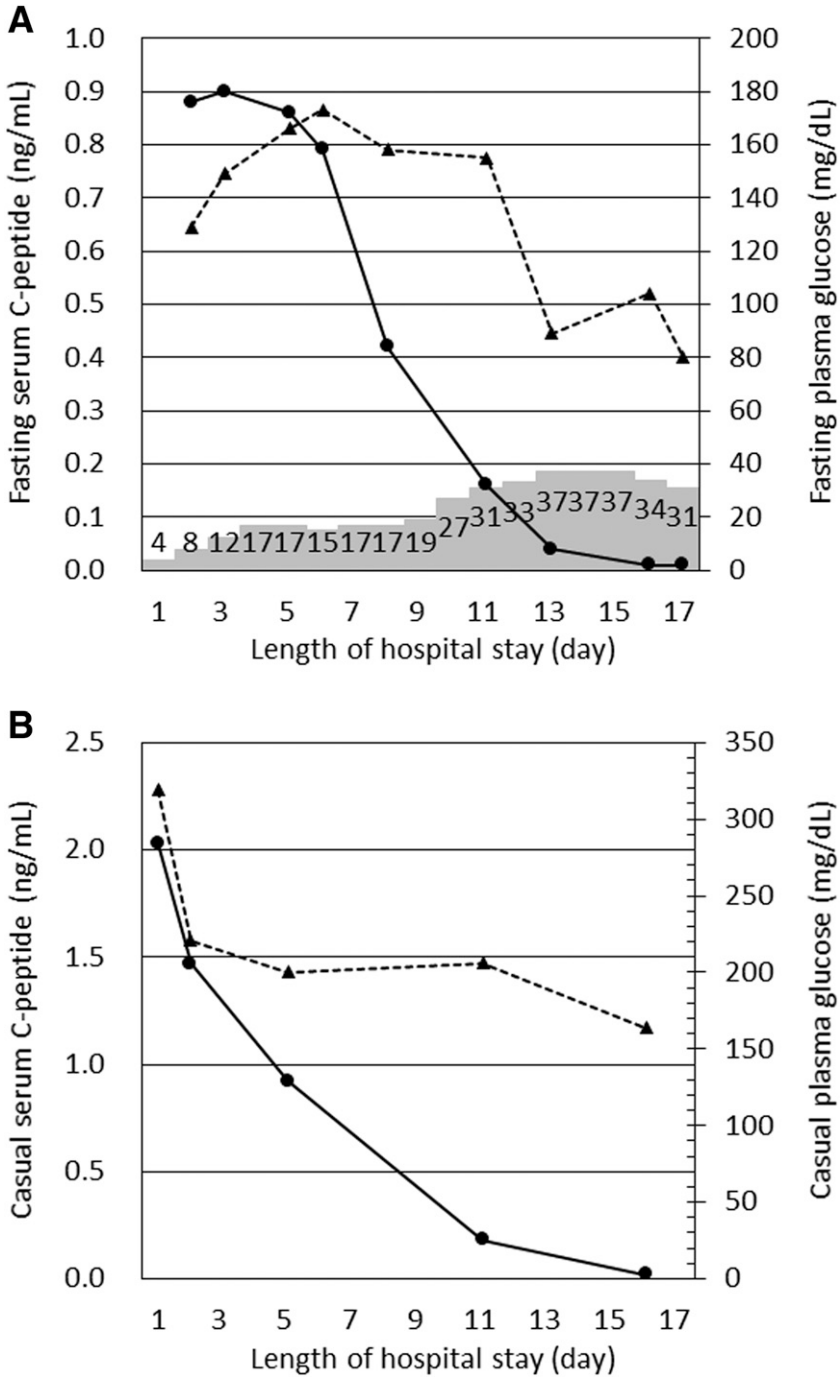

Figure 1—Time course of fasting and casual plasma glucose, fasting and casual serum C-peptide levels, and daily insulin doses after the onset of hyperglycemia. *A*: The *x*-axis shows the length of hospital stay. The *y*-axis on the left side shows fasting serum C-peptide levels, and the *y*-axis on the right side shows fasting plasma glucose levels. The solid line with filled circles represents serum C-peptide levels, and the dashed line with filled triangles represents plasma glucose levels. The shaded area represents daily insulin doses (units/day). The last dose of pembrolizumab was administered 3 weeks before admission. *B*: The *x*-axis shows the length of hospital stay. The *y*-axis on the left side shows casual serum C-peptide levels, and the *y*-axis on the right side depicts casual plasma glucose levels. The solid line with filled circles represents serum C-peptide levels, and the dashed line with filled triangles depicts plasma glucose levels.

point, the HLA in our case, which was not associated with autoimmune T1D, might be related to the negative results, or the use of other islet-associated autoantigens might have obtained different results.

A previous study demonstrated that most patients with T1D caused by pembrolizumab presented with DKA at diagnosis, and all patients with DKA had elevated HbA_{1c} levels (6.85–10.70% [51–93 mmol/mol]), suggesting a certain period of preexisting hyperglycemic state before diagnosis (7). However, considering that our patient was diagnosed with T1D before the occurrence of hyperglycemic symptoms and DKA, the duration of the preexisting hyperglycemic state before diagnosis might have been relatively short, presumably leading to the low HbA_{1c} level (6.1% [43 mmol/mol]) at diagnosis.

We believe it could be clinically beneficial for oncologists, who have an opportunity to use anti–PD-1 drugs, to recognize the time course of β-cell exhaustion in this case.

Duality of Interest. A.Sh. has received lecture fees from Novo Nordisk Pharma Inc., Sanofi K.K., and Eli Lilly Japan K.K. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. D.S. wrote the manuscript. Y.O., Y.Y., Y.I., A.Sa., M.I., S.K., I.I., M.N., and A.Sh. reviewed the manuscript and contributed to discussion. Y.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Imagawa A, Hanafusa T, Awata T, et al. Report of the Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus: new diagnostic criteria of fulminant type 1 diabetes mellitus (2012). J Diabetes Investig 2012;3:536–539
2. Hughes J, Vudattu N, Sznol M, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 2015;38:e55–e57
3. Baden MY, Imagawa A, Abiru N, et al. Characteristics and clinical course of type 1 diabetes mellitus related to anti-programmed cell death-1 therapy. Diabetol Int. 3 July 2018 [Epub ahead of print]. DOI: 10.1007/s13340-018-0362-2
4. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes 2018;67:1471–1480
5. Sekine N, Motokura T, Oki T, et al. Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. JAMA 2001;285:1153–1154
6. Clotman K, Janssens K, Specenier P, Weets I, De Block CEM. Programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus. J Clin Endocrinol Metab 2018;103:3144–3154
7. Cheema A, Makadia B, Karwadia T, Bajwa R, Hossain M. Autoimmune diabetes associated with pembrolizumab: a review of published case reports. World J Oncol 2018;9:1–4