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Case Report

Durvalumab-induced Type 1 Diabetes in a Patient With Pre-existing GADA-positive Diabetes and Preserved Insulin Secretion

Nobuhiro Nakatake,[1] Megumi Matsuda,[1] and Hiroki Kontani[2]

[1]Department of Endocrinology, Kameda General Hospital, Chiba 296-0041, Japan
[2]Department of Medical Oncology, Kameda General Hospital, Chiba 296-0041, Japan

Correspondence: Nobuhiro Nakatake, MD, Kameda General Hospital, 929 Higashi-cho, Kamogawa, Chiba 296-0041, Japan. Email: nakatake.nobuhiro@kameda.jp.

Abstract

Predicting the onset of type 1 diabetes mellitus (T1D) in patients treated with immune checkpoint inhibitors (ICI) remains challenging. ICI-induced T1D (ICI-T1D) is a rare but serious complication that leads to complete insulin depletion. While diabetes-associated autoantibodies, such as glutamic acid decarboxylase antibodies (GADA), are typically absent in non-ICI-related fulminant T1D, they are relatively common in ICI-T1D. However, it is unclear whether these autoantibodies are detectable before the development of ICI-T1D. We present the case of a 61-year-old man with diabetes who had strongly positive GADA and preserved insulin secretion prior to initiating ICI therapy. Following treatment with durvalumab, he developed ICI-T1D, characterized by complete insulin depletion. Notably, the onset of ICI-T1D was precisely tracked on a daily basis, facilitating the timely initiation of insulin therapy and preventing diabetic ketoacidosis. Although the cost-effectiveness of pretreatment GADA screening and intensive monitoring remains a concern, early detection of diabetes-associated autoantibodies and vigilant glucose monitoring after ICI administration may help predict ICI-T1D and enable early therapeutic intervention.

Key Words: immune checkpoint inhibitors, type 1 diabetes, diabetes-associated autoantibodies

Introduction

Currently, immune checkpoint inhibitors (ICI) are widely used to treat various advanced cancers owing to their proven efficacy. Conversely, they are also associated with complications, such as endocrine disorders. It is acknowledged, albeit rarely, that there is an association between ICI and the onset of type 1 diabetes mellitus (T1D), with a frequency of approximately 1% [1]. This can result in the relatively rapid or fulminant depletion of insulin secretion. In cases of fulminant T1D that are not associated with ICI, diabetes-associated autoantibodies such as the glutamic acid decarboxylase antibody (GADA) are typically absent [2]. In contrast, patients with ICI-associated acute-onset T1D (ICI-T1D) are relatively more likely to test positive for diabetes-associated autoantibodies such as GADA. It has been postulated that patients with autoantibodies experience a more rapid onset and higher incidence of diabetic ketoacidosis than those without autoantibodies [3]. Some speculation exists that certain individuals may possess these autoantibodies before the onset of ICI-T1D [3]. However, detailed studies on this issue are scarce, and as a result, the clinical significance of the presence of diabetes-associated autoantibodies prior to ICI administration remains unclear. Herein, we present a case of rapid-onset T1D induced by durvalumab in a patient with diabetes with pre-existing GADA who had preserved insulin secretion before commencing ICI treatment.

Case Presentation

A 61-year-old man was referred to the endocrinology department for treatment of diabetes mellitus and thyrotoxicosis. His medical history revealed no thirst, polydipsia, or nocturnal polyuria suggestive of severe hyperglycemia. However, he lost approximately 9 kg of weight over the previous month without any loss of appetite. On physical examination, a diffuse small goiter was palpable, and finger tremor was noted. The hemoglobin A1c (HbA1c) level was 10.4% (90 mmol/mol) (reference range: 4.9-6.0%, 30-42 mmol/mol), and insulin therapy was initiated. Further detailed evaluation revealed a markedly elevated GADA level of 2000 U/L (reference range: < 5.0 U/L), but a serum C-peptide level was normal at 2.38 ng/mL (0.79 nmol/L) (reference range: 0.80-2.50 ng/mL, 0.26-0.83 nmol/L), indicating preserved insulin secretion. Thyroid function tests showed TSH levels below 0.005 mU/L (reference range: 0.50-5.00 mU/L), free T4 levels of 3.69 ng/dL (47.5 pmol/L) (reference range: 0.9-1.7 ng/dL; 11.6-21.9 pmol/L), suggestive of thyrotoxicosis, and the TSH receptor antibody was positive at 2.2 U/L (reference range: < 2.0 IU/L). Thyroid ultrasound showed no nodular lesions, and the estimated thyroid weight was 25.0 g. Technetium-99 m scintigraphy revealed diffuse thyroid uptake.

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Based on these findings, Graves' disease was diagnosed, and the patient was started on methimazole (15 mg once daily). One and a half years after starting treatment for GADA-positive diabetes with preserved insulin secretion and Graves' disease, the patient was diagnosed with squamous cell carcinoma of the lungs. Chemotherapy including glucocorticoid was administered while the patient was hospitalized in the oncology department. The maximum dose of glargine required to correct glucocorticoid-induced hyperglycemia was 18 units. However, his HbA1c level had already increased to 8.3% before glucocorticoid administration, requiring basal and bolus insulin therapies. After completion of glucocorticoids, the patient's morning fasting blood glucose level was well maintained at approximately 100 mg/dL (5.6 mmol/L) (reference range: 73-109 mg/dL, 4.1-6.1 mmol/L) without basal insulin due to the success of the dietary therapy. The patient was eventually discharged with a minimal dose of liraglutide 0.6 mg. Following discharge, the patient was scheduled to continue chemotherapy in an outpatient clinic and self-monitor blood glucose to manage glucocorticoid-induced hyperglycemia. However, glucocorticoid was not administered in the outpatient department, and the first dose of durvalumab, an anti-programmed cell death ligand 1 (PD-L1) antibody, was administered. In this setting, the patient rapidly developed severe hyperglycemia following durvalumab administration.

Diagnostic Assessment

Until day 15 after durvalumab administration, morning fasting blood glucose levels ranged from 104 to 159 mg/dL but reached 194 mg/dL on day 16 (Fig. 1). Thereafter, hyperglycemia persisted, and mild thirst, polydipsia, and polyuria were observed on day 19. On day 20, a telephone consultation was conducted, and he was started on 4 units of insulin glargine, which he had available at home (Fig. 1). On day 23, the patient's serum C-peptide level was 1.97 ng/mL (0.65 nmol/L); however, by day 28, it had decreased below the detection limit. On the same day, his GADA level decreased from 2000 U/L to 160.2 U/L (Table 1). In addition, islet antigen 2 antibody measured in frozen samples on day 26 was positive at 1.6 U/mL (reference range: < 0.6 U/mL), and zinc transporter 8 and insulin antibodies were negative (Table 1). Human leukocyte antigen (HLA) genotypes were HLA-DRB1*04:05, DQA1*03:03, DQB1*04:01, DPA1*02:02, and DPB1*05:01. Ketosis was observed due to a slight increase in serum beta-hydroxybutyrate of 0.26 to 0.58 mmol/L (reference range: 0-0.074 mmol/L), but ketoacidosis was not observed. Continuous strict insulin administration was not required, and basal-bolus insulin therapy alone was sufficient. Furthermore, thyroid function remained normal with methimazole 5 mg for 5 months before durvalumab administration, and the TSH receptor antibody level was negative at < 2.0 U/L. The patient was scheduled to undergo methimazole tapering. However, on day 33, thyrotoxicosis occurred, with a TSH level of 0.012 mU/L and a free T4 of 2.50 ng/dL (32.2 pmol/L). Additionally, decreased thyroid uptake was observed on technetium-99 m scintigraphy and destructive thyroiditis was diagnosed. Furthermore, the patient had no medical history or laboratory test results suggestive of adrenal insufficiency (data not shown).

Treatment

Insulin glargine was administered starting on day 20 (Fig. 1). During this period, the patient had few symptoms and was in good overall condition with stable vital signs. Consequently, the patient was disinclined to pursue hospitalization for treatment. On day 26, however, his blood glucose reached a high of 673 mg/dL (37.4 mmol/L) (Fig. 1), necessitating an adjustment in the insulin dose under hospitalization. The patient was discharged on a regimen of 16 units of aspart before breakfast, 10 units of aspart before lunch, and 14 units of aspart and 16 units of glargine before dinner. Thyroid hormone replacement therapy was initiated to treat postdestructive hypothyroidism.

Outcome and Follow-up

The patient was administered 30 to 40 units of insulin daily using a continuous glucose monitor in an outpatient setting. His HbA1c level remained in the low 7% range without severe hypoglycemia. We considered the potential benefits of insulin pump therapy as a prospective intervention. For hypothyroidism, 75 μg of levothyroxine was prescribed to maintain optimal thyroid function.

Discussion

In the present study, we observed a case of T1D in which insulin secretion declined markedly following treatment with durvalumab, an anti-PD-L1 antibody, in a patient with GADA-positive diabetes with preserved insulin secretion.

To date, 3 documented cases have been reported in which patients developed GADA before the administration of anti-PD-1 antibodies [4-6]. One of these cases involved a patient with GADA-positive diabetes with preserved insulin secretion before ICI administration, a condition similar to the present case [4]. The remaining 2 patients had not been diagnosed with diabetes before ICI administration; however, they were known to be positive for GADA [5, 6]. All 3 patients developed T1D with rapid insulin depletion within 6 weeks of ICI administration. In this case, blood glucose levels began to rise noticeably on the 16th day following ICI administration, and symptoms such as thirst, polydipsia, and polyuria emerged on the 19th day. The patient engaged in daily self-monitoring of blood glucose, allowing for prompt therapeutic intervention and the avoidance of ketoacidosis.

In Japanese studies, diabetes-associated autoantibodies are typically absent in what is referred to as fulminant T1D that develops independently of ICI [2]. However, it has been reported that GADA, as 1 of the diabetes-associated autoantibodies, is present in approximately 40% to 50% of patients with ICI-T1D, which suggests that GADA may be present before the onset of ICI-T1D [3, 7]. The present case represents a rare instance in which the presence of GADA was known before the onset of ICI-T1D. Furthermore, it has been postulated that patients with GADA may be more susceptible to diabetic ketoacidosis than those without antibodies. This may have resulted in a more rapid decrease in insulin secretion in patients with GADA [3]. Furthermore, in this case, a notable decline in GADA levels was observed following ICI administration from 2000 U/L to 160.2 U/L. Conversely, another case report described a notable increase in GADA titer from 114 U/L to 1160 U/L following ICI administration [4]. Reports indicate a potential correlation between elevated GADA titers and increased risk of insulin secretion depletion in latent

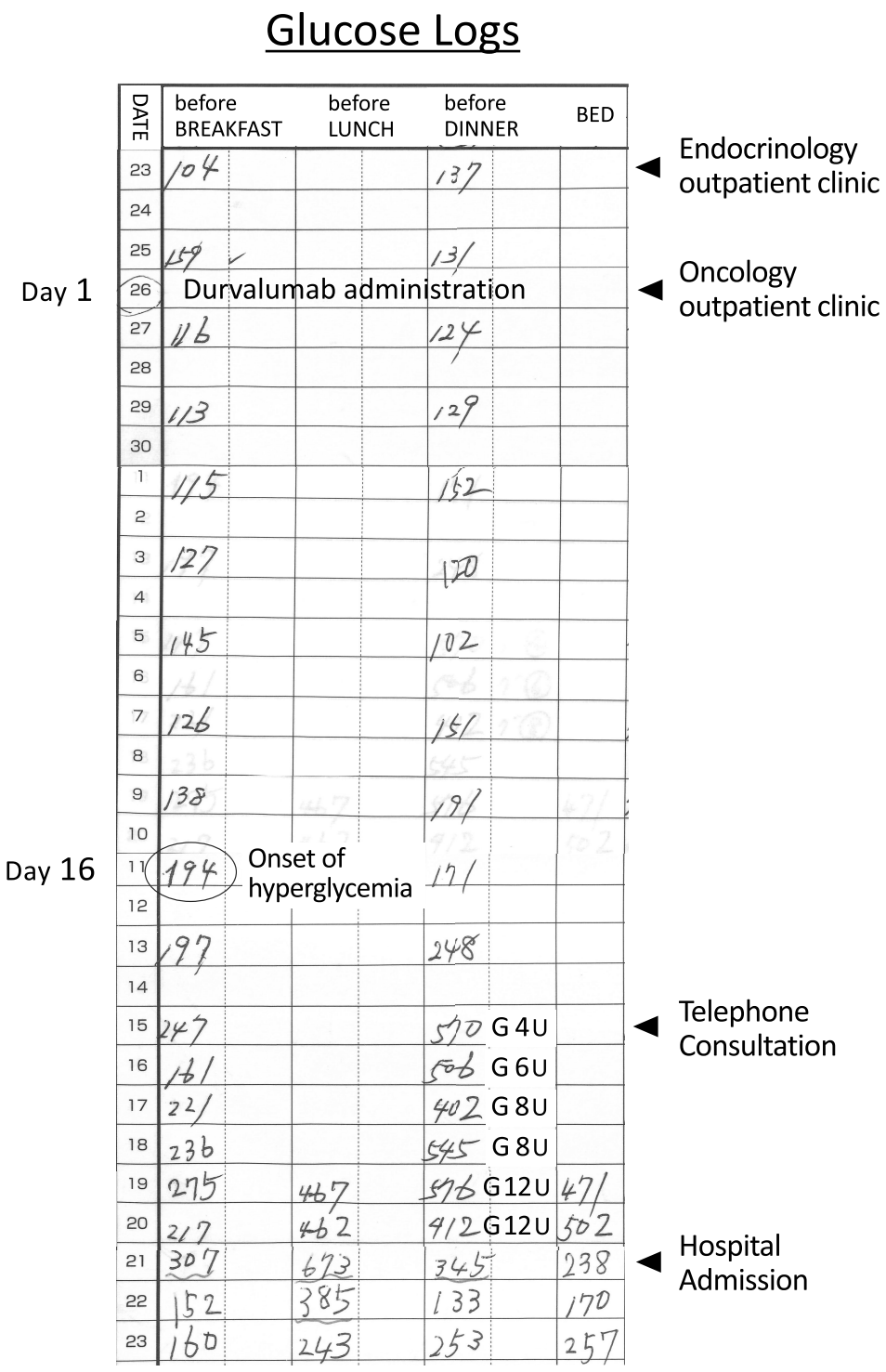

Figure 1. Records of glucose self-monitoring (excerpt from actual patient's glucose log books). Morning fasting blood glucose levels began to rise noticeably on the 16th day following durvalumab administration.

Abbreviations: G, insulin glargine; U, units.

autoimmune diabetes in adults [8]. However, the clinical significance of GADA titers before ICI administration in predicting the onset of ICI-T1D is currently unknown, and further investigation is needed. Although islet antigen 2 antibody was positive in this case, the clinical significance of ICI-T1D requires further investigation.

It has been demonstrated that individuals with ICI-T1D exhibit the presence of high-risk HLA alleles and haplotypes [3, 7]. Examination of the HLA genotypes in this case revealed the presence of HLA-DRB1*04:05, DPA1*02:02, and DPB1*05:01, which have previously been reported to potentially contribute to disease susceptibility in ICI-T1D [9].

ICI-T1D presents as a potentially fatal complication with a rapid onset and difficulty in predicting progression through routine blood glucose monitoring [10]. Early detection of hyperglycemia, which is characterized by symptoms such as

Table 1. Pre- and post- (within 1 month of onset) ICI-T1D laboratory data

Blood tested	Pre-ICI-T1D	Post-ICI-T1D	Reference range
Hemoglobin A1c (%)	6.1-10.4 (43-90 mmol/mol)	7.1 (54 mmol/mol)	4.9-6.0 (30-42 mmol/mol)
Serum C-peptide	1.50-2.61 ng/mL (0.50-0.86 nmol/L)	< 0.15-1.97 ng/mL (< 0.05-0.65 nmol/L)	0.80-2.50 ng/mL (0.26-0.83 nmol/L)
GAD antibody	> 2000U/L	160.2-177.5 U/L	< 5.0 U/L
IA-2 antibody	No data	1.6 U/mL	< 0.6 U/mL
ZnT8 antibody	No data	11.8 U/mL	< 15.0 U/mL
Insulin antibody	No data	< 0.4 U/mL	< 0.4 U/mL
TPO antibody	132 IU/mL	101 IU/mL	< 16 IU/mL
Tg antibody	558 IU/mL	134 IU/mL	< 28 IU/mL
TSH	< 0.005-2.710 mU/L	0.009-0.057 mU/L	0.50-5.00 mU/L
Free T4	0.98-3.69 ng/dL (12.6-47.5 pmol/L)	1.59-2.50 ng/dL (20.5-32.2 pmol/L)	0.9-1.7 ng/dL (11.6-21.9 pmol/L)
TSH receptor antibody	2.2 IU/L	< 1.0 IU/L	< 2.0 IU/L

Values in parentheses are International System of Units.

Abbreviations: GAD, glutamic acid decarboxylase; IA-2, islet antigen 2; ICI-T1D, immune checkpoint inhibitor-induced type 1 diabetes mellitus; Tg, thyroglobulin; TPO, thyroid peroxidase; ZnT8, zinc transporter 8.

thirst, polydipsia, and polyuria, is crucial. Continuous glucose monitoring or daily self-monitoring may improve early identification and intervention, as demonstrated in the current case in which daily self-monitoring facilitated prompt action. Additionally, patients with diabetes-associated autoantibodies, such as GADA, or high-risk HLA genotypes may be particularly vulnerable to rapidly developing progressive T1D after ICI therapy. Although cost-effectiveness remains a concern, high-risk patients should undergo rigorous glucose monitoring to predict and mitigate potentially fatal outcomes. Further studies are required to confirm the utility of these strategies in preventing ICI-T1D-related complications.

Learning Points

- The presence of diabetes-associated autoantibodies such as GADA before ICI administration may indicate an elevated risk of developing ICI-T1D.
- Strict blood glucose monitoring, such as continuous glucose monitoring or daily self-monitoring, may enable early detection of potentially fatal ICI-T1D.
- The identification of HLA genotypes may facilitate the prediction of ICI-T1D onset.

Contributors

All authors contributed individually to authorship. N.N., M.M., and H.K. were involved in patient diagnosis and management. All authors reviewed and approved the final draft of the manuscript.

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Disclosures

The authors have nothing to disclose.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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