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CASE REPORT

Recovery from insulin dependence in immune checkpoint inhibitor-associated diabetes mellitus: A case report

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ABSTRACT

Immune checkpoint inhibitor-associated diabetes mellitus (ICI-DM) is a rare immune-related adverse event and is usually considered permanent. Here, we report the first case of a 54-year-old man with ICI-DM who recovered from insulin dependence. He was diagnosed with lung cancer and started pembrolizumab therapy. After seven cycles, he developed ICI-associated secondary adrenal insufficiency and started hydrocortisone supplementation. Subsequently, he complained of fatigue, and blood examinations showed hyperglycemia with ketosis. A glucagon challenge test indicated insulin dependence. He was diagnosed with ICI-DM and insulin therapy was initiated. Pembrolizumab therapy was discontinued due to concomitant ICI-associated hepatitis. Six months later, a glucagon challenge test result showed an improvement in insulin secretion, and insulin therapy was discontinued. The lung cancer lesions continued to shrink. Even if ICI-DM develops, it might be possible to control the underlying cancer while avoiding lifelong insulin therapy through early discontinuation of ICI.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have led to a paradigm shift in the treatment of cancers[1]. ICIs exert antitumor effects through activating T cells to restore antitumor immunity. However, ICIs are known to cause immune-related adverse events (irAEs) in various tissues, including the endocrine glands. ICI-associated diabetes mellitus (ICI-DM) is a rare irAE characterized as the acute onset of hyperglycemia with severe insulin deficiency that can be fatal if overlooked[2]. β-Cell destruction in ICI-DM is generally considered to be progressive and irreversible, which necessitates lifelong insulin therapy. Here, we report the first case of a patient with ICI-DM who recovered from insulin dependence after ICI discontinuation.

CASE REPORT

A 54-year-old man was diagnosed with stage IVA squamous cell carcinoma of the lung with hilar pulmonary lymph nodes. No medical or family history of any autoimmune or endocrine disease was reported. He received seven cycles of pembrolizumab therapy. A total of 16 days after the last dose, he complained of fatigue and was diagnosed with ICI-associated secondary adrenal insufficiency (Figure 1). A daily maintenance dose of 15 mg hydrocortisone was initiated. A total of 13 days after diagnosis, he complained of fever (38.3°C) and fatigue. Blood examination results showed severe liver dysfunction and hyperglycemia with ketosis (Table 1). His glycated hemoglobin A1c (HbA1c) level was 8.1% and he was negative for diabetes-related autoantibodies. He had no history of diabetes mellitus, and his monthly HbA1c levels were 6.1–6.2% during pembrolizumab administration. His height was 173.2 cm, his bodyweight was 64.7 kg and his body mass index was 21.6 kg/m^2. A glucagon challenge test showed an increment of C-peptide reactivity (ΔCPR) of 0.23 ng/mL (Table 2), and the CPR level in the 24-h urine collection showed a decrease of 17.0 μg/day, suggesting insulin dependence. Computed tomography scans showed no abnormalities in the liver or pancreas. He was diagnosed with ICI-DM and insulin therapy was initiated on admission. Furthermore, he was diagnosed with ICI-associated hepatitis based on a liver biopsy. Pembrolizumab therapy was discontinued, and his liver function improved spontaneously without the need for the administration of steroids. The patient was discharged with an initial total daily dose of 24 units of insulin that was gradually reduced over time. Six months after

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discharge, the total daily dose of insulin was reduced to 12 units, and his HbA1c level was 5.9%, with frequent hypoglycemia. A glucagon challenge test showed an improvement in ΔCPR (1.39 ng/mL; Table 2); therefore, insulin therapy was discontinued. Consequently, his glycemia has been well controlled, with HbA1c levels of 5.9–6.0% for approximately 2 years without medication. The primary and metastatic cancer lesions were reduced after seven cycles of pembrolizumab therapy, and they did not progress further after pembrolizumab had been discontinued.

DISCUSSION

ICI-DM is considered to be due to autoimmune abnormalities and subsequent intense inflammation that leads to the destruction of β-cells[2]. Most patients with ICI-DM show a rapid decrease in endogenous insulin secretion and progress to insulin dependence within a few weeks of onset. Some studies have shown that insulin therapy can be withdrawn after ICI discontinuation; however, these studies did not accurately assess the insulin secretory capacity, and the relevant cases failed to meet the strict definition of ICI-DM[3,4]. The present patient did not have a history of diabetes, but developed hyperglycemia with ketosis at acute onset. We confirmed his insulin dependence using a 24-h urine collection and ΔCPR in the glucagon challenge test at onset[5,6]. He was diagnosed with ICI-DM and insulin therapy was initiated. However, 6 months after pembrolizumab discontinuation, recovery of endogenous insulin secretion was confirmed using a glucagon challenge test and he was able to withdraw from insulin therapy.

Although endocrine irAEs do not require discontinuation of ICI therapy, continuous supplementation of the relevant hormones is required[1]. Patients with ICI-DM generally require lifelong insulin therapy, which adversely affects their quality of life. However, patients with endocrine irAEs have been reported to have a favorable prognosis[7]. The present patient's primary and metastatic cancer lesions were reduced using ICI and they did not progress further. Controlling the underlying cancer while avoiding insulin therapy is likely to be beneficial for such patients.

In the present case, the patient's endogenous insulin secretion at onset was not completely depleted. The presence of residual β-cells at the time of ICI discontinuation might have been important for functional recovery. In a case series involving 22 Japanese patients with ICI-DM, most had decreased serum CPR levels over a period of 2–3 weeks after onset[8]. However, three patients, whose serum CPR levels were maintained to some extent, tended to have increased serum CPR levels for several weeks after ICI discontinuation. Predictors and markers of ICI-DM are important for an early diagnosis. Some relevant predictors include the presence of baseline levels of diabetes-related autoantibodies[7], human leukocyte antigen susceptibility alleles[9] and complications of multiple irAEs[9]. Diagnostic

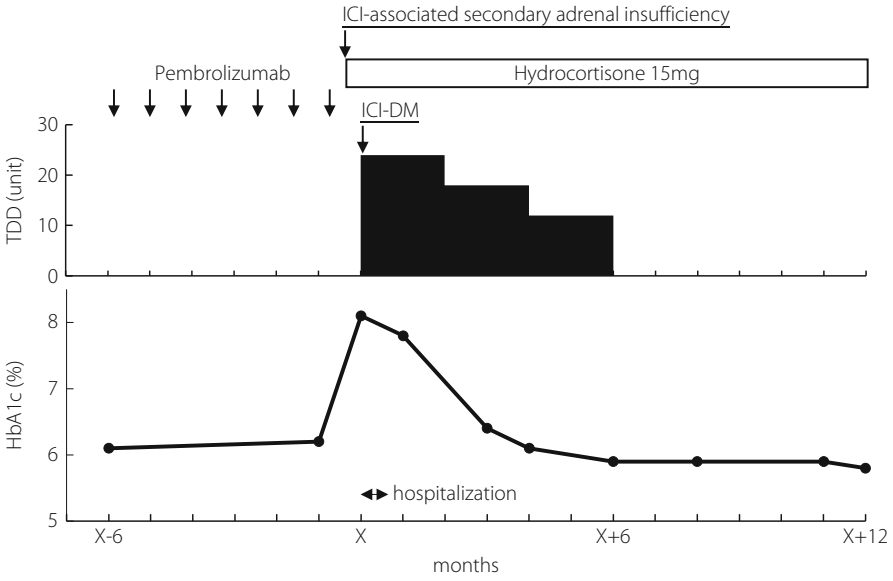

Figure 1 | Time course of the total daily dose (TDD) of insulin and hemoglobin A1c (HbA1c) levels. The patient received seven cycles of pembrolizumab therapy for lung cancer. A total of 16 days after the last dose, he was diagnosed with immune checkpoint inhibitor (ICI)-associated secondary adrenal insufficiency. A daily maintenance dose of 15 mg hydrocortisone was initiated. A total of 13 days after diagnosis (X), he was urgently admitted for severe liver dysfunction and hyperglycemia with ketosis. He was subsequently diagnosed with ICI-associated diabetes mellitus (ICI-DM) and insulin therapy was initiated. He had an initial TDD of 24 units of insulin that was gradually reduced over time. Six months later, the recovery of insulin secretion was confirmed using a glucagon challenge test, and insulin therapy was discontinued. Although his HbA1c levels were 6.1–6.2% during the pembrolizumab administration, they increased to 8.1% at the onset of ICI-DM. After discontinuing insulin therapy, his HbA1c levels reduced to 5.9–6.0% without medication.

Table 1 | Laboratory data

	Results	Reference values
Blood examinations on admission		
White blood cell ($\times 10^3/\mu L$)	5.0	3.9–9.8
Hemoglobin (g/dL)	11.7	13.4–17.6
Platelet ($\times 10^4/\mu L$)	15.1	13–37
Total bilirubin (mg/dL)	0.7	0.2–1.2
AST (U/L)	252	17–59
ALT (U/L)	211	21–72
ALP (U/L)	282	100–340
Amylase (U/L)	54	40–135
BUN (mg/dL)	10.8	8–20
Creatinine (mg/dL)	1.02	0.6–1.1
Sodium (mmol/L)	133	136–148
Potassium (mmol/L)	3.6	3.5–5.3
C-reactive protein (mg/dL)	3.25	0.0–0.5
Fasting glucose (mg/dL)	154	70–110
Total ketone body (μmol/L)	1040.0	26–122
ACAC (μmol/L)	252.0	13–69
3-OHBA (μmol/L)	788.0	<76
Diabetes-related tests		
HbA1c (%)	8.1	4.6–6.2
Glycated albumin (%)	26.4	12.3–16.5
24-h urinary CPR (μg/day)	17.0	40.1–86.1
GADAb (U/mL)	<5.0	<5.0
IA-2Ab (U/mL)	<0.6	<0.6
HLA genotyping	DRB1*09:01-DQB1*03:03 DRB1*08:03-DQB1*06:01	
Endocrinological findings at diagnosis of ICI-associated secondary adrenal insufficiency		
ACTH (pg/mL)	<1.5	7.2–63.3
Cortisol (μg/dL)	0.1	7.1–19.6
TSH (μU/mL)	4.13	0.61–4.23
FT4 (ng/dL)	0.93	0.90–1.70
TgAb (U/mL)	12	0–27
TPOAb (U/mL)	<9	0–15
TRAb (U/L)	<0.8	0–1.9

ACAC, Acetoacetate; ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPR, C-peptide reactivity; FT4, free thyroxine; GADAb, glutamic acid decarboxylase antibody; HbA1c, hemoglobin A1c; HLA, human leukocyte antigen; ICI, immune checkpoint inhibitor; IA-2Ab, islet autoantigen-2 antibody; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; 3-OHBA, 3-hydroxybutyrate.

markers include the presence of specific autoantibodies[7], and elevation of serum amylase and lipase levels[8], in addition to symptoms and quantitative estimations of blood glucose and ketone bodies. The present patient had a susceptible human leukocyte antigen haplotype (DRB1*09:01-DQB1*03:03) for type 1 diabetes, which is frequently detected in patients with ICI-DM[10]. Interestingly, the present patient also had a protective haplotype (DRB1*08:03-DQB1*06:01) for type 1 diabetes[10].

Table 2 | Results of the glucagon challenge test

	0 min	6 min
9 days after admission		
Glucose (mg/dL)	164	179
CPR (ng/mL)	0.63	0.86
6 months after onset		
Glucose (mg/dL)	95	116
CPR (ng/mL)	1.17	2.56

CPR, C-peptide reactivity.

Protective human leukocyte antigen alleles have been reported in some patients with ICI-DM, which might not be robust in patients with ICI-DM[9]. Further studies are required to establish accurate predictors and early diagnostic markers.

In conclusion, although ICI-DM is usually considered permanent, the findings in the present case report suggest that it might be possible to control underlying cancer lesions while avoiding lifelong insulin therapy through early discontinuation of ICI. Further studies are required to investigate how to achieve a balance between controlling underlying cancer and ensuring quality of life.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained directly from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

REFERENCES

1. Johnson DB, Nebhan CA, Moslehi JJ, *et al*. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022; 19: 254–267.
2. Quandt Z, Young A, Anderson M. Immune checkpoint inhibitor diabetes mellitus: a novel form of autoimmune diabetes. *Clin Exp Immunol* 2020; 200: 131–140.
3. Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. *Cancer Immunol Immunother* 2016; 65: 765–767.
4. Trinh B, Donath MY, Läubli H. Successful treatment of immune checkpoint inhibitor-induced diabetes with infliximab. *Diabetes Care* 2019; 42: e153–e154.
5. Matsuda A, Kuzuya T. Urine C-peptide after recovery from diabetic ketoacidosis: an index of insulin dependency. *Diabetes Care* 1982; 5: 581–584.
6. Iwamoto Y, Kimura T, Tatsumi F, *et al*. Glucagon test is a useful predictor of withdrawal from insulin therapy in subjects with type 2 diabetes mellitus. *Front Endocrinol* 2022; 13: 871660.

7. Iwama S, Kobayashi T, Arima H. Clinical characteristics, management, and potential biomarkers of endocrine dysfunction induced by immune checkpoint inhibitors. *Endocrinol Metab (Seoul)* 2021; 36: 312–321.
8. 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* 2018; 101: 58–66.
9. de Filette JMK, Pen JJ, Decoster L, *et al*. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. *Eur J Endocrinol* 2019; 181: 363–374.
10. Yamaguchi H, Miyoshi Y, Uehara Y, *et al*. A case of slowly progressive type 1 diabetes mellitus with drastically reduced insulin secretory capacity after immune checkpoint inhibitor treatment for advanced renal cell carcinoma. *Diabetol Int* 2020; 12: 234–240.