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Case report

Early insulin averts hyperglycemic crisis in slow-onset durvalumab-induced checkpoint inhibitor-associated autoimmune diabetes mellitus

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Abstract

Objective: Checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM), a variant of type 1 diabetes, is a rare immune-related adverse events (irAEs) caused by antibody-based immune checkpoint inhibitors. CIADM typically manifests as fulminant or acute-onset type 1 diabetes in the insulin-depleted state. However, we encountered a patient with slow-onset CIADM who initially presented with hyperglycemia without decreased insulin secretion after treatment with durvalumab (an anti-PD-L1 antibody).
Patient: A 60-year-old man diagnosed with small-cell lung cancer on durvalumab combined with dexamethasone treatment experienced an increase in glycated hemoglobin (HbA1c) from 6.4% to 7.8% after three cycles.
Results: Despite preserved endogenous insulin secretion (C-peptide, 2.47 ng/mL with a casual plasma glucose level of 287 mg/dL), basal insulin therapy was initiated considering CIADM. HbA1c levels remained stable (8.5–9.2%) for 3 months but increased to 13.4% at 18 weeks, indicative of CIADM. Declining endogenous insulin secretion resulted in ketosis; however, hyperglycemic crisis was prevented through basal insulin therapy.
Conclusion: We emphasize that CIADM develops gradually and does not always occur in the course of fulminant or acute-onset type 1 diabetes; therefore, early initiation of insulin in the presence of hyperglycemia is crucial to prevent hyperglycemic crises.

Key words: immune checkpoint inhibitors, durvalumab, type 1 diabetes, autoimmune diabetes, hyperglycemic crisis

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Introduction

Antibody-based immune checkpoint inhibitors (ICIs) targeting anti-cytotoxic T lymphocyte antigen 4 (CTLA-4), anti-programmed cell death 1 (PD-1), or anti-programmed cell death ligand 1 (PD-L1) activate immune cells and exert potent antitumor effects[1]. Although efficacious, immune-related adverse events (irAEs) from treatment remain concerning, with abnormal thyroid function being the most commonly associated autoimmune endocrine disorder. Hypothyroidism and hyperthyroidism is reported in 6.6% and 2.9% of patients, respectively, during ICIs treatment, whereas type 1 diabetes (checkpoint inhibitor-associated autoimmune diabetes mellitus [CIADM]) affects only 0.2%[2, 3].

ICIs-mediated CIADM typically presents as fulminant- or acute-onset type 1 diabetes[4–6], which is commonly diagnosed within 1–12 weeks after the onset of hyperglycemic symptoms[7, 8]. At the time of diagnosis, the mean blood glucose levels often exceed 600 mg/dL, and median serum C-peptide levels are as low as 0.46 ng/mL[4, 9]. However, we encountered a unique case involving a patient treated with durvalumab (an anti-PD-L1 antibody), who initially presented with hyperglycemia despite preserved insulin secretion. Insulin secretion was arrested after 18 weeks, indicative of slow-onset CIADM. Early insulin administration during the insulin-independent phase effectively prevented diabetic ketoacidosis (DKA) in this patient.

Case Presentation

A 60-year-old man with a history of atrial septal defect

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and clinical stage IVA small-cell lung cancer presenting with hyperglycemia was referred to our department. The patient was diagnosed with impaired glucose tolerance before 9 years, with no pertinent family history of diabetes, but was a former smoker until the diagnosis of small cell lung cancer. Dietary assessment by a dietitian revealed a high-fat diet, with an estimated caloric intake of 1,500–2,000 per day. The average body weight was approximately 52 kg (body mass index [BMI] 17.6 kg/m^2), which decreased to 48 kg (BMI 16.2 kg/m^2) following the onset of hyperglycemia.

A routine computed tomography (CT) performed to assess atrial septal defect 1 year before the referral incidentally revealed a tumor in the lower lobe of the right lung along with enlarged lymph nodes in the mediastinum and right pulmonary hilar region. Subsequent diagnostics confirmed small-cell lung cancer (clinical stage: T3N3M1a, Stage IV A, advanced type), and durvalumab plus carboplatin (CBDCA) and etoposide (ETP) chemotherapy was started 2 months before the referral. Dexamethasone (3.3 mg) was administered on days 1 to 3 of each chemotherapy cycle for managing nausea (Figure 1). Before commencing chemotherapy, glycated hemoglobin (HbA1c) level was 6.4%, with a casual plasma glucose (CPG) level of 98 mg/dL. HbA1c levels rapidly deteriorated during treatment, at 7.3% (CPG 170 mg/dL) and 7.8% (CPG 287 mg/dL) during the second and third cycles, respectively. Subsequently, the patient was referred to our department for glucose control.

No hyperglycemic symptoms, such as thirst, polydipsia, or polyuria, were observed, and urine ketones and anti-glutamic acid decarboxylase (GAD) antibodies were negative. Additionally, the levels of serum C-peptide levels (2.47 ng/mL) and CPG (287 mg/dL) indicated that insulin secretory capacity was not completely depleted. Differential diagnoses included steroid-induced diabetes due to dexamethasone administration during chemotherapy and durvalumab-induced CIADM. Insulin glargine U-100 (3 units) was administered subcutaneously before bedtime, and self-monitoring of blood glucose (SMBG) was implemented. The fourth cycle of chemotherapy was administered 1 month after the referral, during which HbA1c and CPG levels worsened to 8.5% and 289 mg/dL, respectively. Consequently, 50 mg of sitagliptin was administered. Despite these measures, HbA1c remained elevated at 8.6% 2.5 months post-referral, prompting a switch to durvalumab monotherapy. Further-

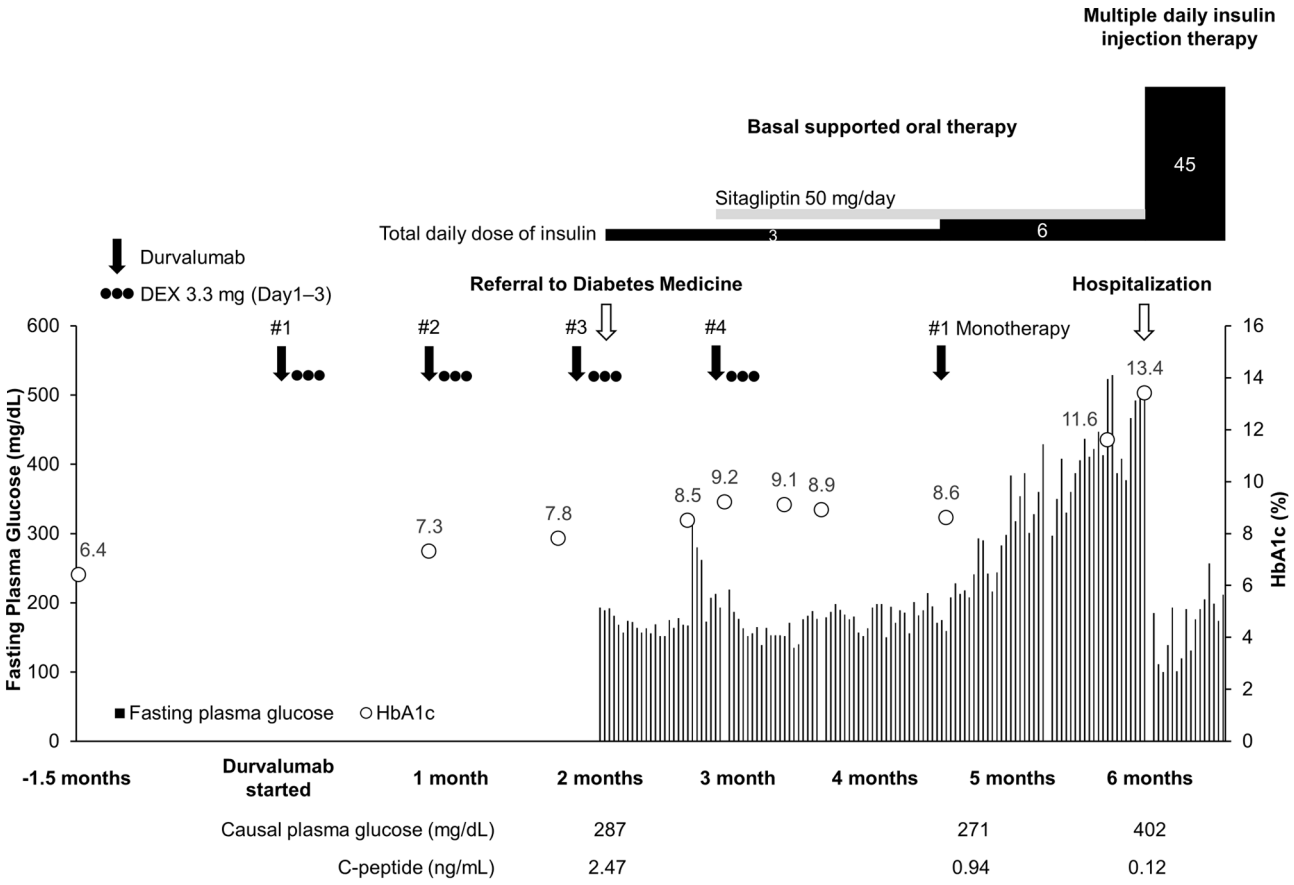

Figure 1 Timeline from the initiation of durvalumab treatment to admission. Band graph shows fasting plasma glucose levels measured by self-monitoring of blood glucose. Circles in the figure represent glycated hemoglobin (HbA1c) values. DEX: dexamethasone.

more, endogenous insulin secretion had decreased, with serum C-peptide of 0.94 ng/dL and CPG of 271 mg/dL. SMBG records indicated a rapid deterioration in blood glucose levels over the preceding 3 months after referral. Subsequently, the insulin glargine U-100 dose increased to 6 units, and hospital admission was recommended. Owing to scheduling constraints, the patient was finally admitted 4 months after the initial referral.

Upon admission, the patient exhibited mild thirst but remained fully conscious. Urine ketone testing was positive, and serum C-peptide was 0.1 ng/mL against a CPG of 402 mg/dL (Table 1). Venous blood gas analysis revealed a pH of 7.363 and a bicarbonate of 22.5 mmol/L, with no evidence of metabolic acidosis. Urine C-peptide over 24 h was measured at 1.1 μg/24 h, and a glucagon test revealed a serum C-peptide that was less sensitive, both before and after stimulation. Anti-GAD, anti-insulinoma-associated protein-2 (IA-2), and anti-zinc transporter 8 (Zn-T8) antibodies were negative. Given that insulin treatment had already been initiated on an outpatient basis, anti-insulin antibodies were not measured. No signs of diabetic neuropathy or nephropathy was observed, and the diabetic retinopathy was limited to the simple type. Amylase and elastase I levels were within the reference range, but lipase levels were mildly elevated. At the time of discharge, 17 days from admission, blood glucose levels had improved; however, endogenous insulin secretion remained decreased, as indicated by a serum C-peptide level of 0.09 ng/mL against a CPG of 196 mg/dL.

We concluded that steroid-induced diabetes was unlikely because glycemic control did not improve after the discontinuation of dexamethasone. Given that the insulin secretory capacity was irreversibly reduced and did not recover even after plasma glucose improvements, it was unlikely that insulin secretion was transiently downregulated because of glucose toxicity from the hyperglycemic state[10]. Although we could not exclude the possibility that spontaneous, classic, and acute-onset type 1 diabetes could have developed coincidentally, we concluded that a CIADM diagnosis was reasonable if the pathogenesis occurred after ICIs administration.

Sitagliptin was discontinued, and multiple daily insulin injections (MDI) were initiated. A dietary plan of 1,800 kcal/day was implemented, along with bolus insulin adjustments and plasma glucose corrections using the carbohy-

Table 1 Baseline laboratory parameters (during admission)

Test	Result	Reference range	Test	Result	Reference range
Complete blood count			Endocrine examination		
White blood cells (/μL)	4,700	4,000–9,000	TSH (μIU/mL)	1.29	0.5–5.0
Hemoglobin (g/dL)	14.2	14.0–18.0	FT4 (ng/dL)	1.7	0.9–1.7
Platelet (10^6/μL)	25.7	15.0–35.0	FT3 (pg/mL)	1.6	2.3–4.0
Blood chemistry			Antibody tests		
Plasma glucose (mg/dL)	402	70–199	Anti-GAD antibody (U/mL)	<5.0	<5.0
C-peptide (ng/mL)	0.12	0.69–2.45	Anti-IA-2 antibody (U/mL)	<0.6	<0.6
HbA1c (%)	13.4	4.6–6.2	Anti-Zn-T8 antibody (U/mL)	<10.0	<15.0
Glycoalbumin (%)	55.7	11–16	Urine test		
Acetoacetic acid (μmol/L)	894	13–69	Specific gravity	1.042	1.01–1.03
3-Hydroxybutyrate (μmol/L)	2,980	0–76	Protein	Negative	Negative
Albumin (g/dL)	4.2	3.8–5.3	Glucose	Positive	Negative
Creatinine (mg/dL)	0.72	0.61–1.04	Ketone bodies	Positive	Negative
Sodium (mEq/L)	133	135–147	Occult blood	Negative	Negative
Potassium (mEq/L)	5.3	3.6–5.0	Urine C-peptide (μg/24 h)	1.1	20.1–155.0
Chloride (mEq/L)	92	98–108	Urine albumin (mg/24 h)	4.9	5.7 ± 2.6
Calcium (mg/dL)	9.3	8.6–10.1	Blood gas analysis (vein)		
Phosphorus (mg/dL)	3.8	2.7–4.5	pH	7.363	—
AST (IU/L)	33	8–38	pCO2 (mmHg)	42.9	—
ALT (IU/L)	31	4–44	Bicarbonate (mmol/L)	22.5	—
LDH (IU/L)	297	124–222	Glucagon stimulating test		
ALP (IU/L)	68	38–113	Fasting plasma glucose (mg/dL)	82	—
GGT (IU/L)	27	12–63	6-minutes plasma glucose (mg/dL)	108	—
Amylase (IU/L)	81	40–126	Fasting C-peptide (ng/mL)	<0.02	—
Lipase (IU/L)	60	13–42	6-minutes C-peptide (ng/mL)	<0.02	—
Elastase substrate I (ng/dL)	234	0–300	—	—	—

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FT3: free tri-iodothyronine; FT4: free thyroxine; GAD: glutamic acid decarboxylase; GGT: gamma glutaryl transferase; IA-2: insulinoma-associated protein-2; LDH: lactate dehydrogenase; pCO2: carbon dioxide partial pressure; pH: potential Hydrogen; TSH: thyroid-stimulating hormone; Zn-T8: zinc transporter 8.

drate counting method. At discharge, the patient was prescribed 3 units of insulin degludec at bedtime, 17–19 units of ultrafast-acting insulin in the morning, 11 units in the afternoon, and 11–12 units in the evening, accounting for a total daily insulin dose of 42–45 units, which stabilized blood glucose levels.

Following discharge, insulin degludec dosage was increased, and bedtime blood glucose correction was added because of elevated nocturnal blood glucose levels, partially attributed to increased lipid intake. CT scans performed at days 112 and 204 after the initiation of durvalumab therapy indicated a reduction in the primary tumor and mediastinal hilar lymph nodes associated with small-cell lung cancer.

Discussion

This case report highlights the challenges in identifying the etiology of hyperglycemia during chemotherapy, particularly when ICIs are combined with steroids, in patients with impaired glucose tolerance. Moreover, this was a rare case with a slow progression of CIADM. Our findings emphasize the importance of prompt insulin therapy to mitigate the risk of hyperglycemic crises such as DKA and hyperosmolar-hyperglycemic states when the cause of glycemic deterioration following ICIs therapy remains unclear.

Age ≥60 years and a history of diabetes were major risk factors for CIADM, with a substantially higher risk reported after four cycles or 3–5 months after ICIs administration[3, 4, 11]. Considering the patient's age, timing of onset, and impaired glucose tolerance in the absence of type 2 diabetes, a diagnosis of CIADM was made. Although islet-associated autoantibodies in CIADM are relatively common in the Western population (71%)[11], the prevalence of anti-GAD antibody-positive cases was lower in the Japanese population (1/21; 4.8%)[4]. Consistent with these findings, our patient was also negative for islet-associated autoantibodies.

In our patient, the period from diabetes diagnosis to the depletion of insulin secretion and onset of ketosis lasted 4 months. Although serum C-peptide level was maintained at 2.47 ng/mL at the time of diabetes diagnosis and was not completely depleted, it decreased to 0.94 ng/mL after 2.5 months. A substantial proportion of patients with CIADM (43.1–59.3%) fulfilled the diagnostic criteria for fulminant type 1 diabetes of the Japan Diabetes Society[4–7]. A study of 21 Japanese patients with CIADM reported that the onset patterns other than fulminant type 1 diabetes met the diagnostic criteria for acute-onset type 1 diabetes[4]. These findings indicate that the timeframe from the onset of hyperglycemia to CIADM diagnosis typically ranges from 1 to 12 weeks[7, 8]. Furthermore, at the time of diabetes diagnosis, serum C-peptide was below 1.1 ng/mL in 83–85% of patients[11, 12] and below 0.3 ng/mL in 63% of patients[5, 6], with a marked decrease observed within 2–3 weeks after diagnosis[4]. In contrast, our patient exhibited a gradual progression (Figure 2). Given that endogenous insulin secretory capacity was preserved at the time of referral, it was difficult to rule out steroids (commonly used for chemotherapy-induced nausea) as a contributing factor causative to the worsening glucose tolerance. However, steroid-induced diabetes manifests as blood glucose levels that normalize after steroid discontinuation. However, this condition may persist, as observed in our patient, despite the addition of insulin or oral diabetes medications, warranting alternative diagnoses. Notably, even high serum C-peptide levels may decrease over time, as observed in our patient.

Our findings indicate that early initiation of insulin therapy may prevent severe sequelae when the type or cause of diabetes remains elusive. At the time of admission, our patient's blood pH was 7.363, indicating no evidence of acidosis, whereas the 3-hydroxybutyrate (3-HB) level was 2.98 mmol/L, which was lower than the 4.5 mmol/L threshold, indicative of mild DKA[13, 14]. Early insulin initiation may inhibit hormone-sensitive lipase activity in the adipose tissue, thereby reducing the production of free fatty acids that serve as substrates for ketone body production[15]. Long-acting insulin significantly suppresses the serum level of 3-HB during discontinuation of continuous subcutaneous insulin infusion in individuals with type 1 diabetes[16]. In addition, pancreatic beta-cell dysfunction is associated with glucotoxicity[17], lipotoxicity due to free fatty acids[18], and endoplasmic reticulum stress[19]. We believe that insulin may attenuate the effects of these pancreatic beta cell-damaging

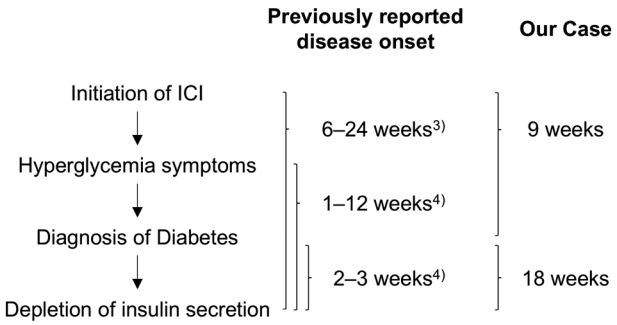

Figure 2 Comparison of the course of checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM) in published reports and our patient. CIADM develops during the course of acute-onset type 1 diabetes or fulminant type 1 diabetes mellitus i.e., the time from the onset of hyperglycemic symptoms to the diagnosis of diabetes with depletion of insulin secretion is within 1–12 weeks (3 months), based on the diagnostic criteria of the Japan Diabetes Society. However, in our patient, the time between the diagnosis of diabetes and the confirmed depletion of insulin secretion occurred at 18 weeks. Superscripts indicate references 3 and 4, respectively.
ICI: immune-checkpoint inhibitor.

factors, thereby inhibiting apoptosis and preserving insulin secretory capacity. Furthermore, a study comparing insulin and sulfonylureas in slowly progressive insulin-dependent diabetes mellitus revealed a significantly lower transition to an insulin-dependent state in the insulin-receiving group[20]. In addition to the possibility that our patient represents a slow-onset course of CIADM, it is likely that the protective effect of early insulin initiation on pancreatic beta cells preserved insulin secretory capacity better than that typically reported in CIADM patients.

Conclusion

Taken together, this case report provides two key insights. First, if hyperglycemia develops within several months, such as in our patient, after the initiation of ICIs treatment without islet-specific autoantibodies or decreases in serum C-peptide levels, early initiation of insulin, even long-acting insulin, can prevent fatal hyperglycemic crises due to CIADM. Second, most patients with ICIs-induced CIADM have a fulminant or acute-onset course. As seen in our patient, insulin secretion may slowly decline before complete depletion, underscoring the importance of early initiation of insulin therapy.

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Consent for publication: We consent to the publication of this report.

Data availability statement: The anonymized patient data used in this study are included in the text.

Author contributions: T.M. was the attending physician. T.M., Y.O., M.S., and H.S. provided both medical care and helped with manuscript preparation. T.M. drafted the manuscript. Y.O., M.S. and H.S. drafted and revised the manuscript. All authors have read and approved the final version of the manuscript for submission.

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