Durvalumab-induced type 1 diabetes mellitus in lung adenocarcinoma: A case report and literature review

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Abstract. Immune checkpoint inhibitor-induced type 1 diabetes mellitus (ICI-T1DM) is a rare adverse reaction associated with durvalumab. Among the adverse reactions to durvalumab, the incidence of new-onset diabetes is relatively rare, occurring in ~0.2% of cases. The present study reports the case of a 62-year-old woman who developed ICI-T1DM following two cycles of durvalumab, presenting with thirst, polydipsia and polyuria. Laboratory examinations (glycated hemoglobin and glutamic acid decarboxylase antibody), along with consultations from an endocrinologist, led to the patient being diagnosed with ICI-T1DM. Immunotherapy was discontinued, and insulin replacement therapy was initiated. Blood glucose levels were closely monitored using a subcutaneous meter. The onset of diabetic ketoacidosis (DKA) was prevented due to timely treatment. In conclusion, medical oncologists need to be aware that durvalumab, an immunotherapy agent, can induce ICI-T1DM. Therefore, regular monitoring of blood glucose levels and collaborative consultations with endocrinologists are essential for an accurate diagnosis when elevated blood sugar levels are detected. The prompt diagnosis of ICI-T1DM is crucial to prevent the occurrence of DKA.

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic approach to cancer treatment. These agents, which include inhibitors targeting programmed cell death protein 1 (PD-1), its ligand programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4, have significantly improved survival outcomes across various malignancies (1). The KEYNOTE-024 trial demonstrated that pembrolizumab significantly improved progression-free survival and overall survival (OS) times compared with chemotherapy in patients with PD-L1-positive advanced non-small cell lung cancer (NSCLC) (2). In the CheckMate 067 clinical trial, patients with advanced melanoma treated with nivolumab plus ipilimumab demonstrated durable responses, with a median OS time of 72.1 months (3). However, ICIs can induce severe immune-mediated toxicities, referred to as immune-related adverse events (irAEs), which can affect the functionality of various organ systems, including ICI-related colitis, pneumonitis, myositis, dermatological toxicity and endocrine toxicity, among others (4). Although endocrine irAEs occur less frequently (10-18%) than dermatological (25-70%) or gastrointestinal (50%) toxicities, they can be severe and, in some cases, irreversible (5,6). Among these endocrine irAEs, ICI-induced type 1 diabetes mellitus (ICI-T1DM) is a rare (<1%) (7) but potentially life-threatening complication characterized by sudden-onset hyperglycemia and insulin deficiency, and frequently presenting with diabetic ketoacidosis (DKA) (8-10). The present study reports the case of a female patient diagnosed with lung invasive adenocarcinoma who developed ICI-T1DM during durvalumab therapy. This case highlights the importance of the early recognition and management of this rare yet critical adverse event, while also providing insights into its clinical presentation, diagnostic challenges and potential underlying mechanisms.

Case report

Patient. The patient, a 62-year-old woman with no prior history of diabetes, was asymptomatic and diagnosed with lung mass lesions by chest computed tomography during a routine health examination (CT) (Fig. 1A and 1B) at China-Japan Friendship Hospital (Beijing, China) in January 2019. In February 2019, the patient underwent a right upper lobectomy and left upper lobe

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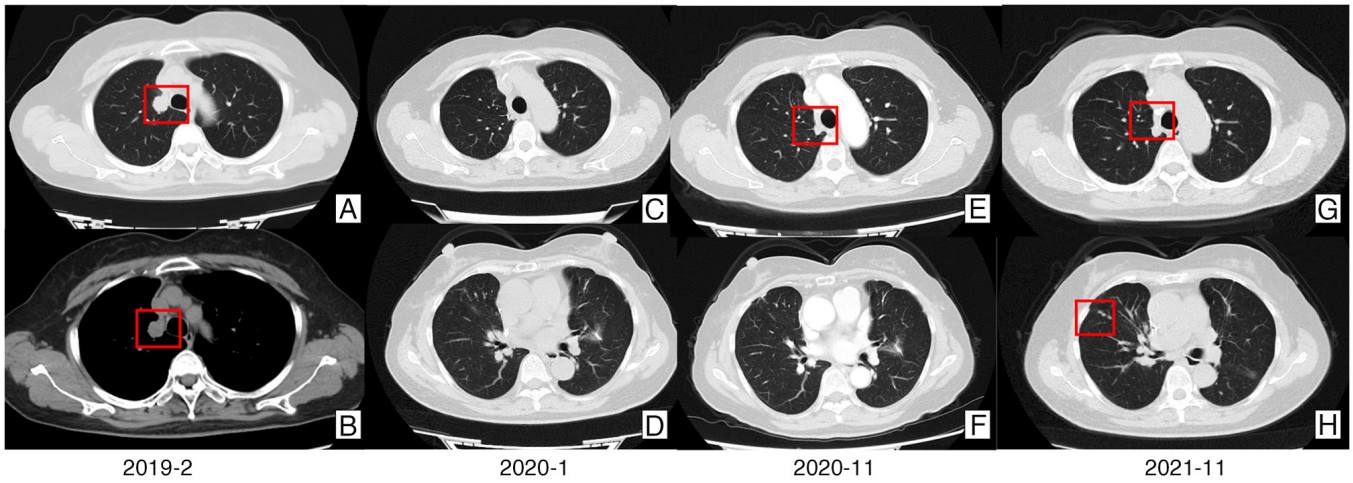

Figure 1. Changes in chest computed tomography during treatment.

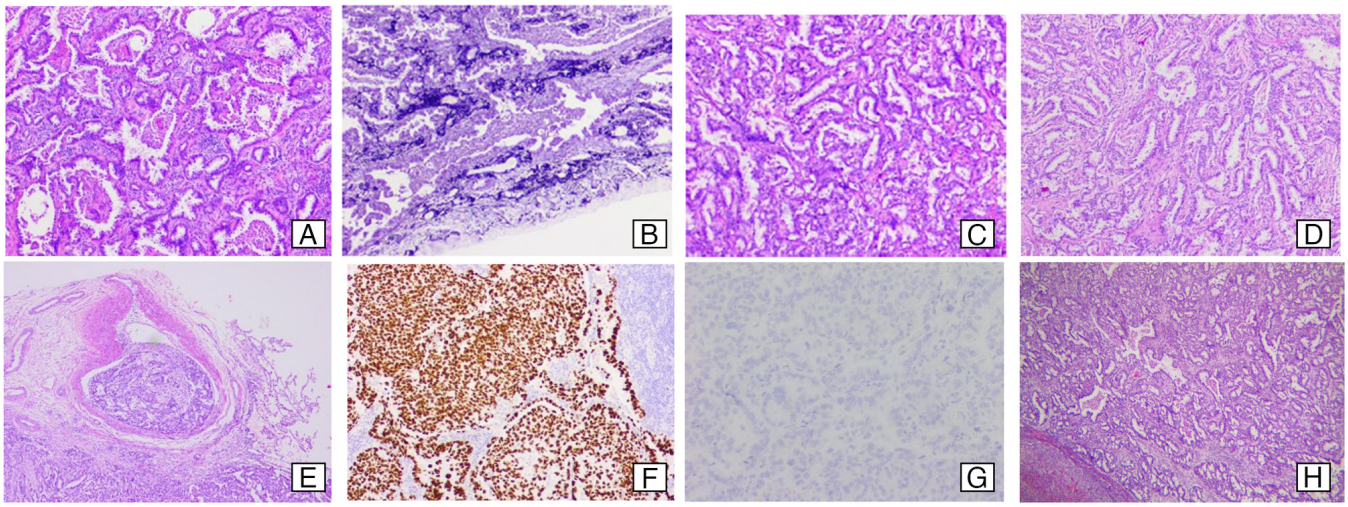

Figure 2. Histopathological images of the patient. (A) An H&E-stained section of invasive adenocarcinoma of the left upper lung nodule (x20 magnification). (B) An elastic fiber stained (iron hematoxylin method) section of the left upper lung nodule (x20 magnification). (C) An H&E-stained section of invasive adenocarcinoma of the right upper lung lobectomy specimen (x20 magnification). (D) An H&E-stained section of invasive adenocarcinoma of the right upper lung lobectomy specimen (x20 magnification). (E) An H&E-stained section of invasive adenocarcinoma of the right upper lung lobectomy specimen showing vascular tumor emboli (x20 magnification). Immunohistochemistry sections were positive for (F) thyroid transcription factor-1 (x20 magnification) and negative for (G) anaplastic lymphoma kinase (x40 magnification). (H) An H&E-stained section of the adrenalectomy lesion (x20 magnification). H&E, hematoxylin and eosin.

wedge resection. Histopathological examinations confirmed invasive adenocarcinoma in the upper lobe of the right lung, diagnosed as stage pT2N0M0 IB according to the 8th edition of the International Association for the Study of Lung Cancer Tumor-Node-Metastasis classification (11), without detectable gene mutations. Additionally, an invasive adenocarcinoma in the left upper lobe was diagnosed as stage pT1N0M0 IA with an EGFR21 mutation. The histopathological and immunohistochemical images of the patient tissues are shown in Fig. 2A-G. H&E-stained sections revealed invasive adenocarcinoma with vascular tumor thrombi. Elastic fiber staining indicated destruction of the pleural elastic lamina. Thyroid transcription factor-1 expression was positive, while anaplastic lymphoma kinase was negative. Targeted therapy with gefitinib was initiated in early March 2019, with oral administration of 250 mg once daily. In late September 2019, a left adrenal tumor resection was performed, with histopathological examinations (Fig. 2H) revealing lung adenocarcinoma metastasis without detectable gene mutations. Following the recurrence of the invasive adenocarcinoma, the patient received three cycles (21-day cycles) of chemotherapy with pemetrexed (800 mg on day 1), carboplatin (400 mg on day 2) and bevacizumab (400 mg on day 1), between November 2019 and ~60 days thereafter. In October 2020 and November 2020, positron emission tomography-CT (Fig. 3) and enhanced chest CT scans (Fig. 1E and F), respectively, showed the recurrence of the malignancy in the right upper hilum. Consequently, the patient was administered 4-6 cycles (21-day cycles) of the following regimen between November 2020 and ~60 days thereafter: Nedaplatin (120 mg on day 1), pemetrexed (800 mg on day 2) and bevacizumab (400 mg on day 2). After December 2020, the patient opted for gefitinib maintenance therapy (250 mg once daily). However, in November 2021, a CT

Table I. Laboratory results.

Laboratory parameter	Value	Reference
Oral glucose tolerance test		
Fasting blood-glucose, mmol/l	17.70	3.61-6.11
Glucose (1 h), mmol/l	24.56	<11.10
Glucose (2 h), mmol/l	30.28	<7.84
Insulin release test		
IRI (0 h), μIU/ml	3.96	2.6-24.9
CPS (0 h), ng/ml	0.96	1.1-4.4
IRI (1 h) μIU/ml	4.14	2.6-24.9
CPS (1 h) ng/ml	0.96	1.1-4.4
IRI (2 h) μIU/ml	4.92	2.6-24.9
CPS (2 h) ng/ml	1.11	1.1-4.4
Other blood laboratory results		
Glycated hemoglobin, %	7.3	4.0-6.0
Glutamic acid decarboxylase antibody, IU/ml	35.02	<10
Islet antigen 2 antibody, IU/ml	<0.7	<10
ALT, IU/l	93	0-40
AST, IU/l	58	0-42
α-amylase, IU/l	108	28-100
Lipase, U/l	34	0-67
Urine laboratory results		
Urine routine glucose	Negative	
Ketone bodies	Negative	

IRI, immunoreactive insulin; CPS, serum c-peptide; ALT, alanine transaminase; AST, aspartate transaminase.

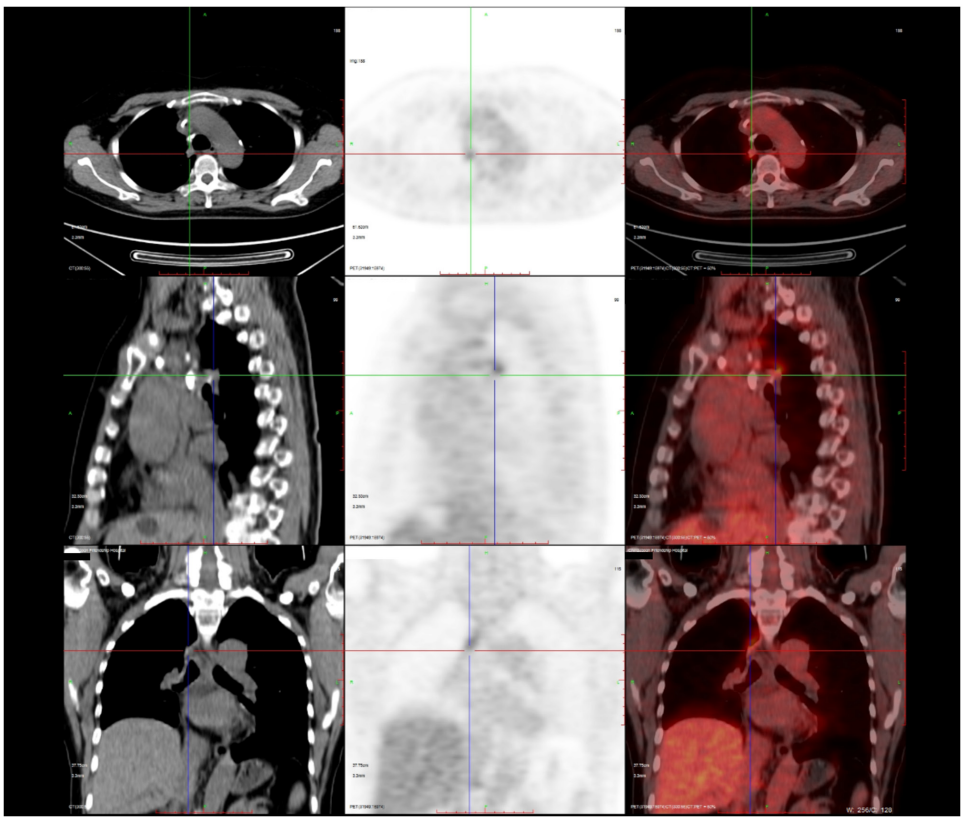

Figure 3. Patient's positron emission tomography-computed tomography scan results from October 2020, indicating recurrence.

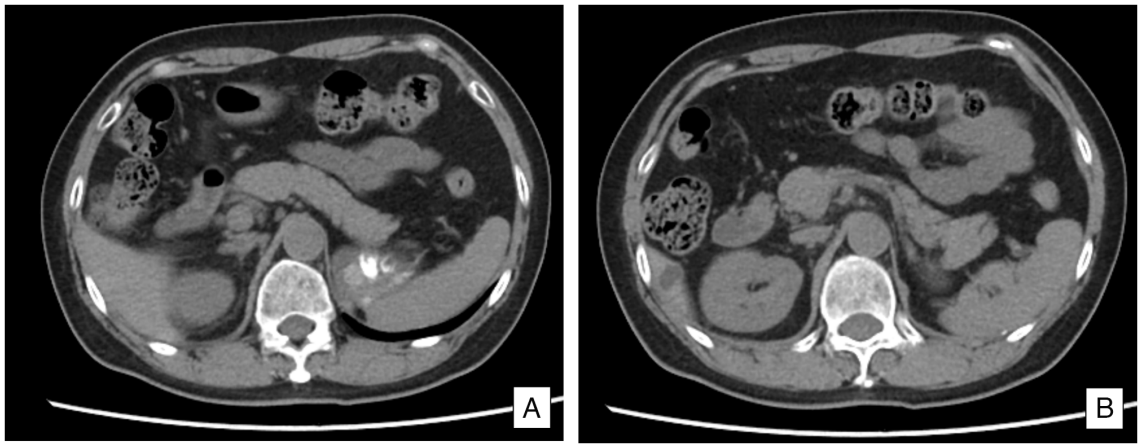

Figure 4. Computed tomography scan of the abdomen. (A) The pancreas is well-defined, with normal size and shape. (B) The surrounding adipose tissue is clearly visible.

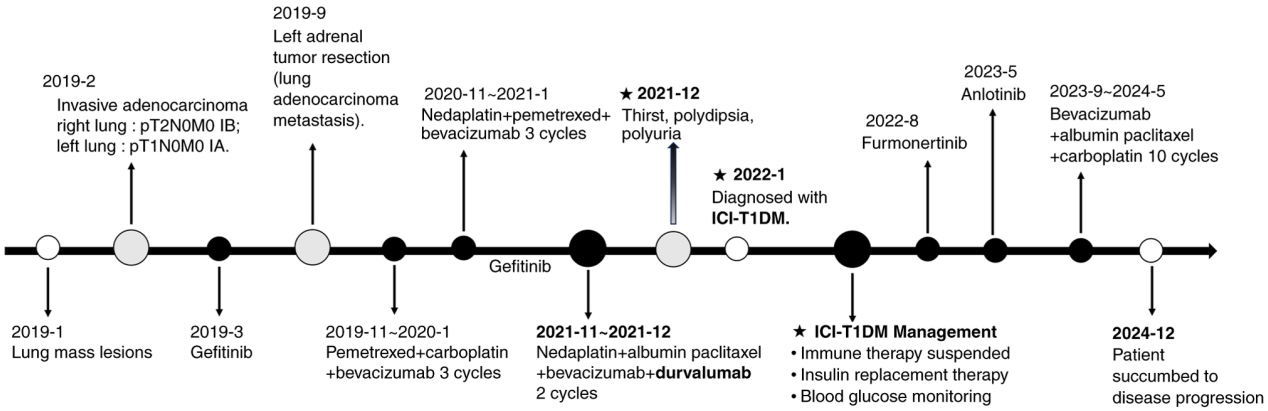

Figure 5. Timeline of diagnosis and treatment. ICI-T1DM, immune checkpoint inhibitor-induced type 1 diabetes mellitus.

scan showed that the disease had progressed (Fig. 1G and H). No pathogenic gene mutations were detected.

Subsequently, on November 2021 and 27 days later, the patient received 1-2 cycles of second-line chemotherapy combined with immunotherapy involving nedaplatin (120 mg on day 1), albumin paclitaxel (200 mg on day 8), bevacizumab (400 mg on day 1) and durvalumab (1,000 mg on day 1). Each cycle lasted 21 days. After experiencing thirst, polydipsia and polyuria since the end of December 2021, the patient sought timely medical attention in January 2022. Given the symptoms and the potential diagnosis of diabetes, a consultation with the Department of Endocrinology was requested for further evaluation. The laboratory abnormalities are shown in Table I. Laboratory tests revealed significantly elevated fasting and postprandial blood glucose levels as follows: Fasting plasma glucose, 17.70 mmol/l; and 2-h postprandial blood glucose, 30.28 mmol/l. The glycated hemoglobin (HbA1c) level was 7.3%. Additionally, the patient's C-peptide level was low and the glutamic acid decarboxylase antibody (GADab) test was positive (35.02 IU/ml), indicating T1DM. A CT scan (Fig. 4) showed that the size and morphology of the pancreas were within normal limits, and the surrounding adipose tissue appeared clear.

Based on the medical history of the patient and the treatment regimen, the patient was diagnosed with ICI-T1DM (12). Subsequently, immunotherapy was discontinued, and the patient was put on insulin replacement therapy, consisting of insulin degludec/aspart (15 IU subcutaneously twice daily) as basal insulin and insulin aspart (15 IU subcutaneously as needed) for prandial coverage. Dosages were titrated according to real-time blood glucose measurements obtained through capillary blood glucose monitoring. After treatment, the patient's fasting blood sugar was maintained within the 5.9-7.5 mmol/l range (normal range, 3.61-6.11 mmol/l). Postprandial levels were as follows: After breakfast, 7.3-11 mmol/l; after lunch, 6.7-8.9 mmol/l; and after dinner, 8.4-10.7 mmol/l (normal range, <11.1 mmol/l). A graphical timeline illustrating the patient's treatment history, durvalumab exposure and the onset of diabetes is shown in Fig. 5. The patient resumed anticancer therapy in August 2022 with oral furmonertinib (80 mg once daily). Monthly follow-ups were conducted at the Department of Integrative Oncology in the China-Japan Friendship Hospital. Due to disease progression, the treatment regimen was subsequently modified to anlotinib (12 mg once daily on days 1-14, every 21 days), followed by bevacizumab (300 mg on day 1) in combination with albumin paclitaxel (200 mg on day 1 and 100 mg on day 8) and carboplatin (300 mg on day 1), administered every 21 days. Ultimately, the patient succumbed to disease progression in December 2024.

Table II. ICI-T1DM caused by anti-PD-1/anti-programmed death ligand 1 treatment in lung cancer.

First author	Year	Age at diagnosis	Sex	Type of tumor	History of diabetes	ICIs	Onset time of ICI-T1DM	Clinical symptoms at onset	Blood glucose, mmol/l	HbA1c%	DKA occurrence	GADab positivity	IA-2ab positivity	Pancreatic enzyme levels	Treatment	(Refs.)
Alrifai, *et al*	2019	69	Male	NSCLC	T2DM	Pembrolizumab	4 cycles (21 days per cycle)	Nausea, vomiting, polyuria, polydipsia, weakness	50.4	9.20	Yes	(+)	No data	No data	Insulin, insulin + metformin	(13)
Capitao, *et al*	2018	74	Female	Lung adenocarcinoma	(-)	Nivolumab	25 days	Polyuria, polydipsia, weight loss, vomiting, confusion, asthenia	58.9	8.70	Yes	(+)	No data	Lipase and amylase increased	Insulin	(14)
Chae, *et al*	2017	76	Male	Lung adenocarcinoma	(-)	Pembrolizumab	2 cycles (21 days per cycle)	Asymptomatic	34.2	6.30	No	(+)	(+)	No data	Insulin	(15)
Chaudry, *et al*	2020	75	Male	NSCLC	(-)	Pembrolizumab	4 cycles (no cycle length mentioned)	Fatigue, severe nausea, weight loss	35.7	No data	Yes	(+)	No data	No data	Insulin	(16)
Cunha, *et al*	2022	59	Female	Lung adenocarcinoma	(-)	Pembrolizumab	3 weeks	Polyuria, polydipsia, weight loss	30.8	5.60	Yes	(+)	No data	(-)	Insulin	(17)
de Filette, *et al*	2019	61	Male	NSCLC	(-)	Pembrolizumab	8 weeks	Nausea, vomiting, diarrhea, generalized weakness	66.3	No data	Yes	(+)	(-)	Lipase increased	Insulin	(18)
Delasos, *et al*	2021	77	Male	High-grade neuroendocrine tumor	(-)	Nivolumab	15 cycles (14 days per cycle)	Fatigue, polyuria, polydipsia	44.5	8.30	Yes	(-)	(-)	No data	Insulin	(19)
Edahiro, *et al*	2019	61	Female	Lung adenocarcinoma	(-)	Pembrolizumab	8 cycles (21 days per cycle)	Emesis, general malaise, thirst	31.8	8.40	Yes	(-)	No data	No normal reference range	Insulin	(20)
Godwin, *et al*	2017	34	Female	NSCLC	(-)	Nivolumab	2 cycles (no cycle length mentioned)	Abdominal pain, nausea, weakness	41.1	7.10	Yes	(+)	(+)	No data	Insulin	(21)
Hatakeyama, *et al*	2019	60	Male	Lung adenocarcinoma	(-)	Nivolumab	36 cycles (14 days per cycle)	Asymptomatic	23.1	9.10	No	(-)	(-)	No data	Insulin	(22)
Huang, *et al*	2021	59	Male	SCLC	(-)	Sintilimab	6 cycles (21 days per cycle)	Polyuria, polydipsia	25.0	7.40	Yes	No data	No data	No data	Insulin	(23)
Ishi, *et al*	2021	51	Male	Large cell carcinoma	T2DM	Nivolumab	14 cycles (no cycle length mentioned)	Not mentioned	57.8	6.90	Yes	(-)	(-)	No data	Insulin	(24)
		62	Male	SCC	(-)	Atezolizumab	15 days	Thirst, vomiting, high fever	21.9	8.90	No	No data	No data	No data	Insulin + antibiotics	
Kedzior, *et al*	2021	51	Female	Lung adenocarcinoma	Not mentioned	Pembrolizumab	2 cycles (21 days per cycle)	Abdominal pain, diarrhea, vomiting, fatigue, dizziness	62.4	8.30	Yes	(+)	No data	No data	Insulin + steroid	(25)

Table II. Continued.

First author	Year	Age at diagnosis	Sex	Type of tumor	History of diabetes	ICIs	Onset time of ICI-T1DM	Clinical symptoms at onset	Blood glucose, mmol/l	HbA1c%	DKA occurrence	GADab positivity	IA-2ab positivity	Pancreatic enzyme levels	Treatment	(Refs.)
Lee, *et al*	2018	67	Male	SCC	T2DM	Nivolumab	2 weeks	Lethargy, polyuria, polydipsia	28.6	7.60	Yes	(+)	(-)	No data	Insulin	(26)
Li, *et al*	2017	63	Male	SCC	(-)	Nivolumab	27 days	Palpitations, fatigue	32.9	7.20	Yes	(+)	No data	No data	Insulin	(27)
Li, *et al*	2020	73	Male	NSCLC	(-)	Anti PD-1	10 cycles (21 days per cycle)	Vomiting, dizzy tachypnea	51.0	7.60	Yes	(-)	(-)	No data	Insulin	(28)
Lupi, *et al*	2019	60	Male	Lung adenocarcinoma	Not mentioned	Atezolizumab	4 cycles (21 days per cycle)	Not mentioned	10 (during L-thyroxine therapy)	No data	Yes	(-)	(-)	No data	Insulin, hydrocortisone, fludrocortisone	(29)
Nishioki, *et al*	2020	73	Female	Lung adenocarcinoma	(-)	Atezolizumab	>4 months	Dysarthria, gait disorder, fatigue, vomiting	53.4	7.30	Yes	(-)	(-)	No data	Insulin	(30)
Patel, *et al*	2019	49	Female	Lung adenocarcinoma	(-)	Durvalumab	3 months	Lethargy, polyuria, polydipsia, blurred vision	21.9	7.80	Yes	(+)	No data	No data	Insulin	(31)
Porntharukchareon, *et al*	2020	70	Male	NSCLC	Not mentioned	Pembrolizumab + ipilimumab	14 weeks	Fatigue, nausea, vomiting	44.1	6.50	Yes	(-)	(-)	(-)	Insulin	(32)
Ren, *et al*	2022	71	Female	SCLC	(-)	Durvalumab	7 months	Asymptomatic	13.9	9.80	No	(-)	(-)	(-)	Insulin	(33)
		61	Female	Lung adenocarcinoma	Not mentioned	Pembrolizumab	6 weeks	Vomiting, difficulty breathing, coma	29.8	No data	Yes	No data	No data	No data	Insulin	
Seo, *et al*	2022	74	Male	Lung adenocarcinoma	(-)	Nivolumab	8 months	Lower stomach discomfort, dysarthria, gait disturbance, lethargy, vomiting	41.0	10.60	Yes	(-)	(+)	No data	Insulin	(34)
Sothornwit, *et al*	2019	52	Female	Lung adenocarcinoma	(-)	Atezolizumab	24 weeks	Not mentioned	18.4	7.90	Yes	(+)	(-)	No data	Insulin	(35)
Tzoulis, *et al*	2018	56	Female	Lung adenocarcinoma	(-)	Nivolumab	3 cycles (14 days per cycle)	Polyuria, polydipsia, disorientated, agitated, combative	47.0	8.20	Yes	(+)	(-)	No data	Insulin	(36)
Yang, *et al*	2022	78	Female	SCLC	(-)	Sintilimab	14 cycles (no cycle length mentioned)	Polyuria, polydipsia	23.4	8.20	No	(-)	(-)	No data	Insulin	(37)
Present study		62	Female	Lung adenocarcinoma	(-)	Durvalumab	2 cycles (21 days per cycle)	Thirst, polydipsia, polyuria	17.70	7.30	No	(+)	(-)	Amylase increased	Insulin	

PD-1, programmed cell death protein 1; ICI-T1DM, immune checkpoint inhibitor-induced type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; DKA, diabetic ketoacidosis; HbA1c, glycosylated hemoglobin type A1C; GADab, glutamic acid decarboxylase antibody; IA-2ab, insulinoma-associated antigen 2 antibody.

Table III. Data analysis of 27 patients from the literature review.

Characteristic	Value
Median age, years	62
Sex, n (%)	
Male	15 (55.56)
Female	12 (44.44)
Disease type, n (%)	
SCLC	3 (11.11)
NSCLC	24 (88.89)
History of diabetes, n (%)	
T2DM	3 (11.11)
Negative	20 (74.07)
Not mentioned	4 (14.81)
ICIs, n (%)	
Pembrolizumab	8 (29.63)
Nivolumab	9 (33.33)
Sintilimab	2 (7.41)
Atezolizumab	4 (14.81)
Durvalumab	2 (7.41)
≥2 types	1 (3.70)
Not clear	1 (3.70)
Time of onset of illness, n (%)[a]	
≤2 months	10 (37.04)
>2 months	17 (62.96)
Symptoms, n (%)	
Vomiting	11 (40.74)
Polydipsia	11 (40.74)
Fatigue	10 (37.04)
Polyuria	9 (33.33)
Consciousness disorder	6 (22.22)
Nausea	5 (18.52)
Weight loss	3 (11.11)
Abdominal pain	2 (7.41)
Diarrhea	2 (7.41)
DKA, n (%)[b]	
Yes	22 (81.48)
No	5 (18.52)
Mean HbA1c, %	7.95
Mean blood glucose, mmol/l[b]	38.83
Antibodies, n (%)	
GADab$^+$	13 (48.15)
IA-2ab$^+$	3 (11.11)

ICI, immune checkpoint inhibitor; T2DM, type 2 diabetes mellitus; NSCLC, non-small cell lung cancer; DKA, diabetic ketoacidosis; HbA1c, glycosylated hemoglobin type A1C; GADab, glutamic acid decarboxylase antibody; IA-2ab, insulinoma-associated antigen 2 antibody. [a]GADab positivity was significantly associated with the onset timing of new-onset ICI-T1DM (P=0.005, Mann-Whitney U test). [b]There was no significant association between GADab and blood glucose levels (P=0.462, t-test) or the occurrence of DKA (P=0.560, Fisher's exact test).

Methods

Tissue staining. Specimens were fixed for 24 to 48 h in 10% neutral-buffered formalin at room temperature and embedded in paraffin. The tissue blocks were sliced into 4- or 5-μm thick sections. H&E staining was performed using hematoxylin for 10 min and eosin for 5 min at room temperature. The elastic fibers were stained using the iron hematoxylin method, also at room temperature. 5% Ethanol hematoxylin, 10% ferric chloride and Verhoeff's iodine solution were mixed at a ratio of 20:8:8 drops, and then dropped onto the tissue section. Counterstaining was performed with eosin for 2 min.

Immunohistochemistry was performed by EnVision system. Antigen retrieval was performed using high pressure at 120˚C for 5 min, and endogenous enzyme activity was blocked with 3% H_2O_2 for 10 min. The primary antibodies were ALK (clone D5F3; catalogue number, K18082; Roche Diagnostics) and TTF-1 (clone SPT24; catalogue number, 18092706; OriGene Technologies, Inc.), both with a dilution ratio of 1:200, incubated at room temperature for 1 h. The secondary antibody was horseradish peroxidase labeled polymer (dilution ratio, 1:2,000; catalogue number, M00855-M01010; Roche Diagnostics), incubated at 37˚C for 30 min. Next, DAB was used for color development, and hematoxylin was used for counterstaining for 10 min. All sections were observed using a light microscope.

Literature review

To contextualize this case, a literature review was conducted in the PubMed database (https://pubmed.ncbi.nlm.nih.gov). The following search strategy was used: [‘Lung Neoplasms’(Mesh) OR ‘Lung Cancer’ OR ‘NSCLC’ OR ‘SCLC’] AND (‘Nivolumab’ OR ‘Pembrolizumab’ OR ‘Atezolizumab’ OR ‘Durvalumab’) AND (‘Type 1 Diabetes’ OR ‘T1DM’) AND [‘Case Reports’(Publication Type) OR ‘case report’ OR ‘case series’]. The literature search was conducted on August 15, 2023, covering all eligible articles from database inception to the search date. Inclusion criteria were as follows: Case reports or case series with a clear diagnostic basis confirming patients with ICI-T1DM. Exclusion criteria included non-peer-reviewed literature (e.g., preprints and conference abstracts), case reports with incomplete data and articles for which the full text was unavailable. This literature review aimed to collect case reports of ICI-T1DM associated with anti-PD-1/PD-L1 therapy in patients with lung cancer. After data retrieval, a total of 25 case reports involving 27 patients were identified (13-37). The author, year, patient's age and sex, medical history, pathological type, ICIs administered, time of disease onset, symptoms, blood glucose levels, HbA1c percentage, GADab status, insulinoma-associated antigen 2 antibody (IA-2ab) status, pancreatic enzyme levels, whether the condition presented with DKA and treatment modalities, among other parameters. Key clinical characteristics, including onset time, symptoms and treatment, are summarized in Table II. The corresponding information of the patient in this study is also provided in Table II for comparison purposes.

The PubMed database was systematically reviewed to identify case reports of ICI-T1DM, selecting studies based on predefined criteria, including confirmed diagnosis and documented clinical course. The analysis indicated that

early-onset cases are more frequently associated with pancreatic autoantibody positivity and that PD-1 inhibitors may be linked to a higher incidence of ICI-T1DM compared with PD-L1 inhibitors. Nearly one-half of the patients (48.15%) tested positive for GADab. Notably, two patients with positive GADab and IA-2ab developed ICI-T1DM during the second cycle. However, further studies are needed to validate these trends. Collectively, most of the 27 patients were diagnosed with non-small cell lung cancer. Additionally, 23 patients presented with a median HbA1c level of 7.90% (mean, 7.95%; range, 5.60-10.60%). Vomiting and polydipsia were the most common, followed by fatigue, polyuria and consciousness disorder (lethargy, coma and confusion). Approximately 81.48% of the patients presented with DKA at the first diagnosis. Statistical analysis was performed using SPSS version 25 (IBM Corp.). The normality of quantitative data was assessed using the Shapiro-Wilk test. Normally distributed data were compared between groups with independent samples t-tests, while non-normally distributed data were analyzed using the Mann-Whitney U test. Categorical data were examined with χ^2 or Fisher's exact tests. $P<0.05$ was considered to indicate a statistically significant difference. The results revealed that there was no significant association between GADab and blood glucose levels (P=0.462) or the occurrence of DKA (P=0.560). However, GADab positivity was significantly associated with the onset timing of new-onset ICI-T1DM (P=0.005). The characteristics of the 27 patients are summarized in Table III.

Despite these novel observations, this literature review has certain limitations. First, given that this study is based on case reports, characterized by a small sample size and lack of a control group, the generalizability of the findings is limited. Second, variations in diagnostic criteria and follow-up durations across the included reports introduce potential heterogeneity, which poses significant challenges to the interpretation of the results. Additionally, since case reports are retrospective studies, certain clinical parameters may lack standardized definitions across different studies. Consequently, future research should focus on conducting larger-scale cohort studies, establishing standardized diagnostic criteria and extending follow-up durations to validate our findings and provide more reliable clinical guidance.

Discussion

The patient in this study had no prior history of diabetes or hyperglycemia during previous cancer treatments. However, after immunotherapy, the patient showed an elevated blood glucose level, islet dysfunction (with serum C-peptide below the normal range) and absolute insulin deficiency, among other complications. These observations exhibited a positive temporal association with durvalumab. The likelihood of this event was assessed using the Naranjo Adverse Drug Reaction Probability Scale (38), which yielded a score of 6, which indicates a probable relationship. Additionally, according to a previous report, the incidence of new-onset diabetes associated with ICIs in patients exposed to PD-L1 inhibitors alone was 0.73% (8). New-onset diabetes is a rare adverse effect of durvalumab, occurring in only 0.2% of cases (39). Among the 27 patients included in this review, only 2 received durvalumab. All the patients exhibited a history of ICI treatment. Vomiting and polydipsia are the most common symptoms (13,14,18,24,30,33,34,40). The initial symptoms experienced by this patient included thirst, polydipsia and polyuria without vomiting. Additionally, compared with the 81.48% of patients who developed DKA, as presented in Table II, the current patient did not present with DKA at the time of diagnosis, likely due to the early recognition of symptoms and timely medical consultation.

Notably, ICI-T1DM is a distinct subtype of T1DM, primarily triggered by pancreatic β-cell destruction due to ICI therapy (41). Under normal physiological conditions, the PD-1/PD-L1 pathway protects pancreatic β-cells from immune cell toxicity by inducing T-cell apoptosis. However, previous studies have shown that ICI therapy disrupts the interaction between PD-L1 molecules on pancreatic β-cells and PD-1 receptors on autoreactive T cells, thereby inhibiting their binding (42). Consequently, autoreactive T cells evade elimination and damage β-cells. Therefore, PD-1 inhibition leads to T-cell activation and subsequent destruction of pancreatic β-cells. During this process, $CD8^+$ T cells function as the primary effector cells. Previous studies on the pancreatic pathology of patients with ICI-T1DM have shown an increase in $CD8^+$ T cells and a reduction in the macrophage population (43-46). Research indicates that activated autoreactive T cells respond to PD-1 inhibition by releasing interferons (IFNs). These IFNs activate monocyte-derived macrophages (44). When treated with anti-PD-L1, cytotoxic IFN-γ^+ $CD8^+$ T cells infiltrate the islets and induce the dedifferentiation of pancreatic β-cells (45). These T cells utilize nitric oxide to kill pancreatic β-cells, leading to insulin deficiency and the development of ICI-T1DM. This condition, ICI-T1DM, presents with distinct clinical manifestations, disease features and pathogenic factors compared to the traditional T1DM, therefore it warrants differentiation clinically (47). The incidence of DKA in ICI-T1DM is higher compared with that in traditional T1DM, and its presence is frequently associated with other irAEs (44,48). Additionally, in the case of ICI-T1DM, there is no spontaneous remission period (49). Moreover, there are inducements of pancreatic autoimmunity before the onset of ICI-T1DM. Patients with ICI-T1DM may also exhibit elevated trypsin levels (50,51).

GADab and IA-2ab are biomarkers of pancreatic autoimmunity and potentially play significant roles in predicting ICI-T1DM. GADab is an enzyme involved in the synthesis of the neurotransmitter γ-aminobutyric acid and is also a major pancreatic islet autoantibody (52). GADab is the most commonly used diagnostic marker for adult T1DM. In ICI-T1DM, the interval between the initiation of anti-PD-1/PD-L1 antibody treatment and the onset of ICI-T1DM is associated with the presence or absence of GADab (52). The literature review indicated that the onset of ICI-T1DM in patients with positive GADab results was earlier, ~2 months on average, compared with the onset in patients with negative results for the pancreatic islet antibody (52). These observations are consistent with the present case report, in which the patient was GADab-positive and the onset time was within 6 weeks. IA-2ab is also an important marker of pancreatic autoimmunity. Studies have shown that IA-2ab is present in ~60% of patients with newly diagnosed T1DM (53). However, in ICI-T1DM, the significance

of IA-2ab is less pronounced compared with that of GADab. A systematic review revealed that 18% of patients with ICI-T1DM tested positive for IA-2ab, compared with 51% for GADab (18). In another retrospective analysis involving 10 patients with ICI-T1DM, IA-2ab levels were found to be within the normal range (54). This suggests that the predictive role of IA-2ab in ICI-T1DM requires further investigation. A study revealed that at least one pancreatic autoantibody was positive in 53% of patients with ICI-T1DM, and two or more autoantibodies were detected in 15% of patients (18). Therefore, pancreatic autoantibody serological testing may be conducted before the initiation of ICI therapy to help predict the onset of ICI-T1DM.

Given the absence of typical clinical symptoms and reliable predictors for ICI-T1DM, as well as the life-threatening risks associated with rapid onset and delayed treatment, clinicians must remain vigilant. Regular blood glucose monitoring is essential, and when elevated blood sugar levels are detected, a timely and accurate differential diagnosis should be made in conjunction with endocrinologists. Following an accurate diagnosis of ICI-T1DM, immunosuppressant administration should be discontinued and replaced with insulin replacement therapy. Currently, it is believed that the occurrence of ICI-T1DM does not contraindicate the continuation of ICI therapy, provided that blood glucose levels can be effectively controlled through insulin therapy. Therefore, the treatment and follow-up of diabetes should be continued after the temporary cessation of ICI treatment. Decisions regarding temporary interruption or permanent discontinuation of ICI therapy must be guided by an individualized risk-benefit assessment. Furthermore, the decision to restart ICI therapy after achieving stable blood glucose control should be made collaboratively by oncologists and endocrinology experts.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HD and SL participated in study design and wrote the original manuscript draft. XZ, JZ, YP and XL obtained medical images and analyzed patient data. CX, YZ and YY analyzed pathological images and made the diagnosis. ZH contributed to the follow-up and data analysis. YP participated in language revision of the manuscript. HC was involved in drafting the manuscript, revising it critically for important intellectual content, data analysis and giving final approval of the version to be published. HD and SL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript

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