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Original Research

Clinical characteristics and outcomes of immune checkpoint inhibitor-induced diabetes mellitus

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ABSTRACT

Objective: To better understand immune checkpoint inhibitor (ICI)-induced diabetes mellitus (DM) in cancer patients.

Design and method: We present a case of ICI-induced diabetic ketoacidosis (DKA) and conduct a systematic review of the PubMed and Web of Science databases up to September 2021 to identify all published cases of ICI-induced diabetes.

Results: In addition to our case, a total of 171 published cases were identified during the literature search. Summary and statistical analyzes were conducted for all 172 cases. The median onset time from ICI initiation to DM diagnosis was 12 weeks (range: 0–122). DKA was present in 67.4% (116/172) of the cases, and low C-peptide levels were detected in 91.8% (123/134), indicating an acute onset of diabetes. Patients with positive glutamic acid decarboxylase antibodies (GADA) had an earlier onset of ICI-induced diabetes (median time 7 weeks vs. 16 weeks for GADA-negative patients, $p < 0.001$) and a higher frequency of DKA development (82.8 vs. 62.1%, $p = 0.006$). All but two patients developed insulin-dependent diabetes permanently. Immunotherapy rechallenge was reported in 53 cases after glycemia was well controlled.

Conclusion: ICI-induced DM is a serious adverse event that often presents with life-threatening ketoacidosis. GADA positivity is related to an earlier onset of ICI-induced diabetes and a higher frequency of DKA development. Close monitoring of glucose levels is needed in patients receiving ICI treatment. ICI-induced DM is usually insulin-dependent since damage to β cells is irreversible. On the premise of well-controlled glycemia, immunotherapy rechallenge is feasible.

Introduction

Immune checkpoint inhibitors (ICIs), which commonly target immune checkpoints (e.g., programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4)), unleash the power of the immune system to eradicate tumor cells. The response rate of ICIs ranges from 15 to 60% in advanced malignancies [1]. Despite the benefits for oncology treatment, activation of the immune system could induce a variety of autoimmune effects known as immune-related adverse events (irAEs).

Since a large proportion of patients do not respond to ICIs, it is necessary to identify biomarkers that predict which patients derive the most benefit. Predictive biomarker research has predominantly been focused on tumor mutational burden, PD-L1 expression, microsatellite instability-status, gut microbiota, and irAEs [2,3]. Most studies have concluded that patients with irAEs experience improved outcomes, but some studies have come to the opposite conclusion [1]. The relationship between irAEs and ICI efficacy has not been fully revealed. In particular, whether the irAE site, severity, onset time and management have an impact on ICI effectiveness deserves further exploration.

IrAEs affect a wide spectrum of organs and systems [4], commonly endocrine, pulmonary and dermatologic systems [5]. Among all these irAEs, ICI-induced diabetes mellitus (DM) is a rare but potentially life-threatening one and deserves further attention. ICI-induced DM, also known as ICI-related autoimmune diabetes, is thought to be similar to type 1 diabetes mellitus (T1DM), but the mechanism has yet to be fully elucidated. The occurrence of ICI-induced DM in both clinical trials and real-world studies ranged from 0.9 to 1.9% [6–9]. Most of these

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cases presented as fulminant diabetes with an extremely acute onset, which could result in a life-threatening hyperglycemic hyperosmolar state or diabetic ketoacidosis (DKA) [10]. Furthermore, the pancreas exhibits not only endocrine but also exocrine functions. Patients with ICI-related pancreatic injury could present with diabetes, pancreatitis, or both. The relationship between the two types of pancreatic injuries remains unclear. It is important to study ICI-induced DM and to identify a possible link between diabetes and lipase/amylase elevation. In recent years, cases reporting ICI-induced DM have increased gradually, making it possible for us to learn more about this special disease.

Case presentation

A 43-year-old man with extensive small cell lung cancer and no history of diabetes was enrolled in the CS1003-102 trial on Jan 21, 2020. His body mass index and baseline serologic workup, including random blood glucose, serum amylase and serum lipase, were within the normal range. He was initially treated with CS1003 (anti-PD-1 monoclonal antibody, Cstone Pharmaceuticals, China) plus the combination of etoposide and carboplatin for 4 cycles followed by CS1003 monotherapy every 3 weeks for long-term maintenance. A continuous partial response was achieved after 2 cycles of treatment until the last follow-up on March 16, 2022. The patient complained of mild upper abdominal pain before cycle 3 treatment. On March 17, 2020, laboratory findings revealed elevated serum amylase and pancreatic lipase levels of 158 U/L (upper normal limit (UNL) 115 U/L) and 1179 U/L (UNL 393 U/L), respectively. Contrast-enhanced computed tomography (CT) scans of the pancreas were normal (Fig. 1). Immune-related pancreatitis was suspected, and octreotide and proton-pump inhibitors were subsequently prescribed to the patient. Both serum amylase and lipase decreased to the normal range on March 22, and his abdominal pain was relieved. Cycle 3 treatment was given as scheduled.

On April 3, 2020, the patient was transferred to the emergency room with a 2-day history of polyuria, polydipsia, burning pain of the upper abdomen, fatigue, and drowsiness. Physical examination revealed impaired consciousness, dry mouth, marbled skin, cold extremities, hypotension (blood pressure: 105/45 mmHg) and tachycardia (heart rate: 108 beats per minute). Blood analysis showed marked hyperglycemia (47.19 mmol/L). Arterial blood gas analysis showing severe metabolic acidosis with respiratory compensation, together with the positive reaction of urinary ketones, supported the diagnosis of DKA. Extended biological investigations revealed glycated hemoglobin (HbA1c): 7.6%, fasting C-peptide <0.05 ng/mL, and negative T1DM-related autoantibodies. Thyroid-stimulating hormone (TSH) was slightly low, while free triiodothyronine (FT3) and free thyroxine (FT4) were in the normal range (Table 1). No HLA-typing test was performed. The patient recovered from DKA after receiving an intravenous insulin pump and intravenous fluid treatment for approximately 10 days and was prescribed subcutaneous insulin injection sequentially for long-term treatment.

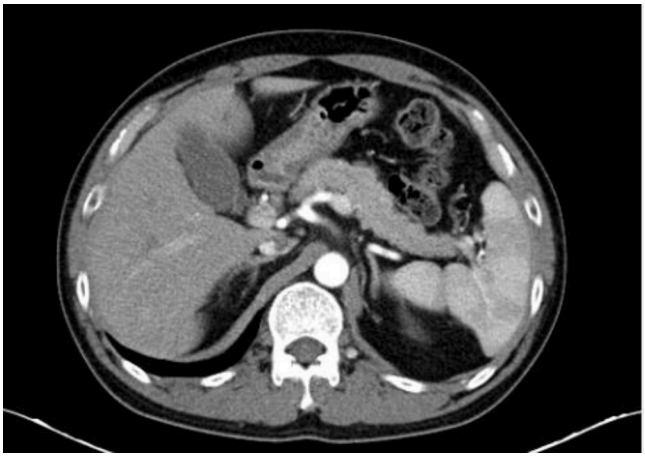

Fig. 1. Contrast-enhanced computed tomography (CT) scans of the pancreas were normal.

Routine tests after 4 cycles of chemoimmunotherapy showed that TSH decreased and FT3 rose to 7.46 pg/mL, without any related clinical symptoms. Thyroid peroxidase antibody (TPO-Ab) and thyroid-stimulating immunoglobulin were negative. Based on these laboratory findings, the patient was diagnosed with ICI-induced thyroiditis. However, his thyroid dysfunction returned to normal spontaneously about two months later without further intervention or suspending PD-1 antibody.

After 15 cycles of anti-PD-1 monotherapy, he developed a new cough with yellow sputum, combined with shortness of breath in April 2021. Chest CT revealed new patchy shadows in both lungs (Fig. 2). Electronic bronchoscopy suggested that the bronchial mucosa was smooth, and etiological screening of sputum and bronchoalveolar lavage fluid (BALF) was negative. BALF cytological classification showed that the number of lymphocytes was elevated significantly, which matched the diagnostic criteria of immunotherapy-associated pneumonia, and immunotherapy was consequently suspended. Prednisone (40 mg per day) was prescribed, and the dosage of subcutaneous insulin was increased accordingly. Since pulmonary infection could not be ruled out completely, moxifloxacin was also given for two weeks. Ten days later, a CT scan suggested that the patchy shadows were absorbed, and prednisone was reduced slowly.

Methods

The PubMed and Web of Science databases were searched up to September 2021 for case reports and case series on the subject of DM and ICIs. The title and abstract were screened for manuscript selection. Language was restricted to English. Congress reports were excluded. The search terms included ‘CTLA-4’, ‘PD-1’, ‘PD-L1’, ‘Pembrolizumab’,

Table 1
Laboratory data on admission.

Lab test results	Value	Reference
Serum		
Glucose, mmol/L	47.19	3.9–6.1
Urea, mmol/L	3.21	2.78–7.14
Creatinine, μmol/L	56	59–104
Na, mmol/L	134	135–145
K, mmol/L	3.8	3.5–5.5
Cl, mmol/L	98	96–111
Ca, mmol/L	2.0	2.13–2.70
Albumin, U/L	34	35–52
Total bilirubin, μmol/L	16	5.1–22.2
ALT, U/L	16	9–50
IAA	<2	<20
ICA	2.55	<20
GADA	<2	<10
IA2A	<2	<10
C-peptide, ng/mL	<0.05	0.8–4.2
HbA1c,%	7.6	4.5–6.3
FT3, pg/mL	1.92	1.8–4.1
FT4, ng/dL	1.37	0.81–1.89
TSH, μIU/mL	0.291	0.38–4.34
Urine ketones, mmol/L	>=7.8	Negative
Arterial blood gas		
pH	7.27	7.35–7.45
$PaCO_2$, mmHg	22	35–45
PaO_2, mmHg	118	83–108
HCO_3^-, mmol/L	9.6	22–27

ALT, glutamic-pyruvic transaminase; IAA, insulin autoantibody; ICA, islet cell autoantibody; GADA, glutamic acid decarboxylase autoantibody; IA2A, insulinoma-associated antigen-2 autoantibody; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

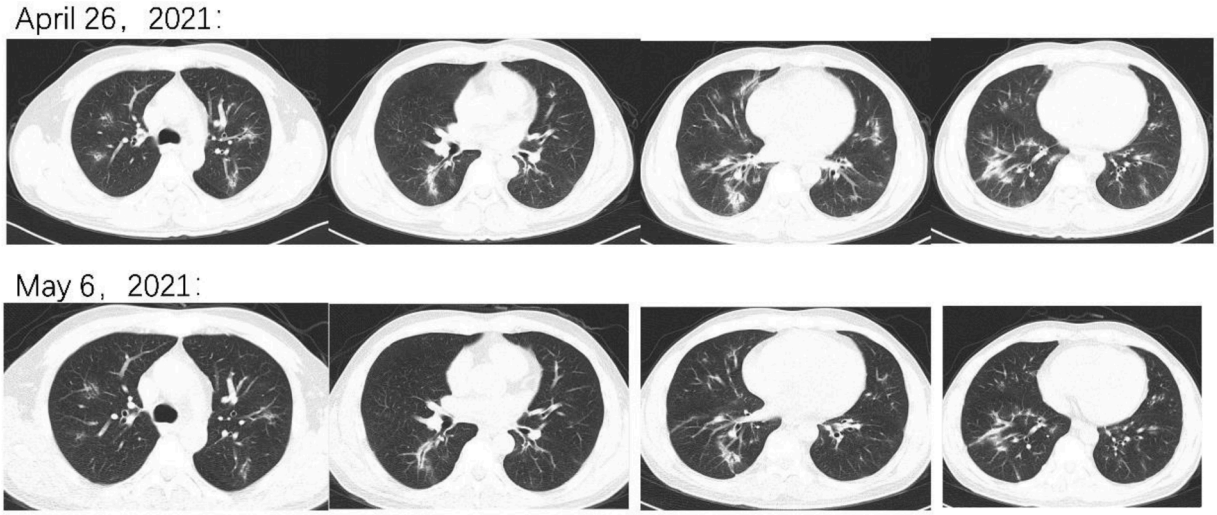

Fig. 2. CT on April 26, 2021 showed patchy shadows in both lungs. CT on May 6, 2021 showed that the previous patchy shadows had regressed.

'Nivolumab', 'Ipilimumab', 'Atezolizumab', 'Durvalumab', 'immune checkpoint inhibitors', 'cancer immunotherapy', 'diabetes mellitus', 'autoimmune diabetes', 'diabetic ketoacidosis', 'ketoacidosis', 'DKA', and 'fulminant diabetes'. The following data were extracted from each manuscript: author, year of publication, sex and age of the patient, cancer type, checkpoint inhibitor therapy, relevant past medical history, onset time of diabetes, presence of DKA, glycemia, HbA1c, C-peptide, islet autoantibodies, serum lipase or amylase, development of other irAEs, and ICI rechallenge. Statistical analysis was carried out using the SPSS Statistics software program (version 24.0; IBM Corporation, Armonk, NY).

Results

Literature search identified a total of 151 studies, of which 102 studies were eligible. Baseline characteristics are presented in Table 2. In addition to our patients, 171 cases were identified [7,8,11–110], with a male predominance (106/172, 61.6%) and a median age of 63 years (range 12–87). A prior diabetes history was observed in 13.4% (23/172) of the patients. Four patients had been exposed to high-dose glucocorticoids before DM diagnosis. The main tumor types were melanoma (43.6%) and lung cancer (30.2%). Pancreas metastasis was reported in two cases. Most patients were treated with anti-PD-1 or anti-PD-L1 monoclonal antibodies as monotherapy (76.2%). A total of 15.7% (n = 27) of the patients received a combination therapy of anti-PD-1/PD-L1 and CTLA-4 blockade and 6.4% (n = 11) of the patients received chemoimmunotherapy. Fifty-nine cases reported tumor regression or stable disease in response to the treatment.

The median time from initiation of ICIs to diabetes diagnosis was 12 weeks (range: 0–122). One patient with previous type 2 diabetes treated with a sodium-glucose cotransporter-2 (SGLT2) inhibitor presented with DKA two days after the first dose of pembrolizumab [29], which is the shortest duration reported between immunotherapy initiation and ICI-induced DM diagnosis. The contribution of the SGLT2 inhibitor remains uncertain since published cases of DKA in the setting of combined SGLT2 and PD-1 inhibitors are rare. Six patients reported ICI-induced DM 6-14 weeks after the suspension of ICIs, including two patients [77,86] who developed diabetes during sequential treatment with ipilimumab after nivolumab. To our knowledge, no case of immune-related diabetes induced by anti-CTLA-4 antibody alone has been reported, and it is reasonable to assume that the above two cases of diabetes were mainly caused by nivolumab.

The presentation of DM related to cancer immunotherapy often follows a severe course. A total of 67.4% (116/172) of the patients presented with DKA, with a median presenting glycemia of 32.0 mmol/L (range: 10.0–109.4) and glycated hemoglobin of 8.0% (range: 6.0−13.7%). One developed a hyperosmolar hyperglycemic state. Low C-peptide levels were present in 91.8% (123/134) of the cases. Among these cases, C-peptide levels were found to be normal in 10 patients at

Table 2
Baseline characteristics of patients with ICI-induced diabetes mellitus.

Characteristics	No. of Patients (%) or median (range) (N = 172)	
Age (years)	63 (12–87)	
Male	106 (61.6)	
History of diabetes	23 (13.4)	
Exposure to high-dose glucocorticoids	4 (2.3)	
Tumor types		
Melanoma	75 (43.6)	
Lung cancer		52 (30.2)
Renal cell carcinoma		10 (5.8)
Breast cancer		6 (3.5)
Gastrointestinal cancer		6 (3.5)
Lymphoma		5 (2.9)
Hepatocellular carcinoma		2 (1.2)
Others		16 (9.3)
Pancreas metastasis	2 (1.2)	
Immunotherapy		
Pembrolizumab		65 (37.8)
Nivolumab		59 (34.3)
Atezolizumab		3 (1.7)
Durvalumab		1 (0.6)
Other PD-1/PD-L1 monoclonal antibody		3 (1.7)
Nivolumab + Ipilimumab		21 (12.2)
Pembrolizumab+ Ipilimumab		6 (3.5)
ICI + chemotherapy		11 (6.4)
Other combination therapy*		3 (1.7)
Clinical tumor response		
CR/PR/SD		59
PD		2
NA		111

*Includes anti-PD-L1+CD137 blockade, atezolizumab+interleukin-2 and durvalumab+ Bacillus Calmette–Guérin.
PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available.

the onset of diabetes but decreased below the reference range during follow-up. In two cases, C-peptide levels obtained post ICI-induced DM were in the normal range [34,74], indicating preserved β cell function. These two patients were finally able to discontinue insulin therapy, while all other reported cases were insulin dependent. Nine patients had normal C-peptide levels at the time of diabetes diagnosis without being retested later. Glucocorticoids were applied in 5 cases to salvage β cell function, but all failed. It should be noted that C-peptide levels of these 5 patients were below normal at the time of glucocorticoids initiation. Serum lipase or amylase levels were elevated in 46.7% (28/60) of the analyzed patients. Immunotherapy rechallenge was reported in 53 cases after glycemia was well controlled. Forty-six patients ceased ICIs definitely due to DM/DKA (7), multiple irAEs (9), progressive disease (10), financial issues (1) or unreported reasons (19) (Table 3). None of the patients died of ICI-induced DM or DKA.

A total of 44.8% of the cases reported other irAEs apart from diabetes, and thyroiditis, rash, and hypophysitis were the most reported (Table 3). At least one of the islet autoantibodies was positive in 46.4% (70/151), while two or more autoantibodies were detected in 7.3% (11/151) of the cases. The most common antibody was glutamic acid decarboxylase autoantibody (GADA), which was positive in 42.4% (64/151) of patients, followed by islet cell autoantibody (ICA) in 12.0%, insulin autoantibody (IAA) in 11.9%, insulinoma-associated antigen-2 autoantibody (IA2A) in 6.9%, and zinc transporter 8 autoantibody (ZnT8A) in 4.4%. An overview of islet autoantibodies is shown in Table 4.

The onset of ICI-induced diabetes appeared earlier for patients presenting with DKA (median time 10 weeks vs. 18 weeks for patients without DKA, $p = 0.013$), positive islet autoantibodies (8 weeks vs. 16 weeks for autoantibody-negative patients, $p < 0.001$) or elevated lipase/amylase (9 weeks vs. 15 weeks for patients with normal lipase/amylase, $p = 0.027$). The rate of developing DKA was 82.8% among GADA-positive patients and 62.1% among GADA-negative patients ($p = 0.006$). The median glycemia at diagnosis was higher for patients with elevated lipase/amylase (44.0 vs. 30.0 mmol/L) or DKA (35.3 vs. 21.0 mmol/L). A summary of the results can be found in Table 5.

Table 3
Disease characteristics of patients with ICI-induced diabetes mellitus.

Disease characteristics	No. of Patients (%) or median (range) ($N = 172$)	
Time to diagnosis (weeks)	12 (0–122)	
Glycemia (mmol/l)	32.0 (10.0–109.4)	
HbA1c (%)	8.0 (6.0–13.7)	
Diabetes ketoacidosis	116 (67.4)	
C-peptide level		
	Low or undetectable	123/134 (91.8)
	Normal*	11/134 (8.2)
	NA	38
Lipase/amylase		
	Elevated	28/60 (46.7)
	Normal	32/60 (53.3)
	NA	112
Positive diabetes autoantibodies		
	None	81/151 (53.6)
	At least one	70/151 (46.4)
	Two or more	11/151 (7.3)
	NA	21
Coexisting irAEs	77 (44.8)	
	Thyroiditis/thyroid dysfunction	53 (30.8)
	Dermatitis/rash	12 (7.0)
	Hypophysitis	9 (5.2)
	Others	26 (15.1)
Rechallenge of ICIs		
	Yes	53 (30.8)
	No	46 (26.7)
	NA	73 (42.4)

* Two patients had normal C-peptide levels after ICI-induced diabetes development, the other nine patients had normal C-peptide levels at the time of diabetes diagnosis without being retested later.
HbA1c, glycated hemoglobin; NA, not available; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events.

Table 4
Diabetes-related autoantibodies and ICI-induced diabetes.

	Positive	Negative	NA	Frequency,%
All	70	81	21	46.4
GADA	64	87	21	42.4
ICA	3	22	147	12.0
IAA	7	52	113	11.9
IA2A	8	108	56	6.9
ZnT8A	2	43	127	4.4

ICI, immune checkpoint inhibitor; GADA, glutamic acid decarboxylase autoantibody; ICA, islet cell autoantibody; IAA, insulin autoantibody; IA2A, insulinoma-associated antigen-2 autoantibody; ZnT8A, zinc transporter 8 autoantibody; NA, not available.

Discussion

In this study, we report a patient with small cell lung cancer who received an anti-PD-1 antibody and developed rapid onset diabetes with ketoacidosis following lipase elevation. Moreover, we conduct a systematic review of 172 cases (171 published cases in addition to the case presented herein) of ICI-induced DM and summarize the clinical characteristics of these patients. Our results showed that 67.4% of the patients presented with a fulminant onset of DKA at the time of ICI-induced DM diagnosis. Positive islet autoantibodies were reported in approximately half of the tested cases (70 out of 151 or 46.4%), with GADA being the predominant antibody. This result is consistent with a previously reported rate [9,111] and differs from "classic" T1DM, where autoantibodies are present in 80−95% of patients [112,113]. In addition, patients with islet autoantibodies, regardless of the type of autoantibody, showed a significantly shorter duration between ICI initiation and ICI-induced diabetes ($p < 0.001$). Furthermore, GADA positivity is related to an earlier onset of ICI-induced diabetes ($p < 0.001$) and a higher frequency of DKA development ($p = 0.006$), possibly indicating a different mechanism of diabetes development between autoantibody-positive and autoantibody-negative patients. Autoantibodies have been recognized as risk factors for irAEs, for example, TPO-Ab in thyroid dysfunction and islet antibodies in ICI-induced DM [99]. This is possibly because ICIs could both facilitate preexisting autoantibody-mediated immunity and trigger the production of autoantibodies by enhancing B-cell immunity [114].

What our case distinguishes from other ICI-induced DM patients as well as the key point that bewildered physicians is that the case presents as elevation of amylase and lipase at first. It is rare for patients to develop ICI-induced pancreatitis and ICI-induced DM sequentially. ICI-induced DM is presumably caused by immune destruction of pancreatic β cells. Both preclinical evidence from mouse models and pancreatic pathological results showed that PD-1-PD-L1 signaling and CD8+ T lymphocyte infiltration play an important role in ICI-induced DM [115–118]. Studies about the mechanism of how ICI-induced pancreatitis occurs are rather limited. However, increased peripancreatic CD3+ T lymphocyte and CD8+ T lymphocyte infiltration may also contribute to the development of pancreatitis, as has been reported in ICI-induced DM patients [119]. Although the mechanism underlying the collateral damage between exocrine pancreatic inflammation and β islet cells remains elusive, future research should examine the possibility of sequential damage from exocrine to endocrine pancreatic function. Upon noticing elevated levels of amylase or lipase, clinicians should not

Table 5
Comparison between patients with or without islet autoantibodies, elevated lipase/amylase levels and DKA.

	Islet autoantibodies			GADA			Lipase/amylase levels			DKA		
	Positive (*N* = 70)	Negative (*N* = 81)	P value*	Positive (*N* = 64)	Negative (*N* = 87)	P value*	Elevated (*N* = 28)	Normal (*N* = 32)	P value*	Yes (*N* = 116)	No (*N* = 56)	P value*
Onset time (weeks)	8	16	**0.000**	7	16	**0.000**	9	15	**0.027**	10	18	**0.013**
Glycemia (mmol/L)	33.8	31.7	0.925	34.0	31.4	0.492	44.0	30.0	**0.007**	35.3	21.0	**0.000**
HbA1c(%)	7.9	7.8	0.656	7.9	7.8	0.969	7.8	7.6	0.232	8.0	8.2	0.338
Lipase elevation	10/21	17/37	0.902	9/18	18/40	0.724	–	–	–	–	–	–
DKA	55/70	52/81	0.053	53/64 (82.8)	54/87(62.1)	**0.006**	23/28	19/32	0.055	–	–	–

* U test or chi-square test.
GADA, glutamic acid decarboxylase autoantibody; DKA, diabetes ketoacidosis; HbA1c, glycated hemoglobin.

only monitor the enzymes and imaging of the pancreas but also monitor the blood glucose of patients receiving ICIs. The elevation in amylase might be a sign of the onset of fulminant DKA.

ICI-induced DM has been generally characterized by a sudden onset, loss of insulin secretion and high rate of DKA. Due to its acute disease progression, steroids are not effective when β islet cells are destroyed completely. Thus, the current measure to treat ICI-induced DM is insulin injection, similar to type 1 diabetes. The case we present rechallenged ICI after recovery from DKA. Moreover, the onset of irAEs may reflect a better prognosis in patients receiving ICIs. Our patient achieved a 2-year major partial response of small cell lung cancer, which also adds evidence to the relationship between irAE incidence and better treatment response in cancer patients.

There are several limitations of our study. The sample size was small, and the analysis included individual patient data, of whom not all parameters of interest were available. The incidence of ICI-induced DM could not be calculated by the lack of the total number of treated patients. Moreover, since data were collected from published literature, there may be publication bias resulting in a higher calculated incidence of DKA. Nevertheless, we systematically reviewed the cases reported in the literature and provided a better understanding of ICI-induced DM patients. Further studies of the mechanism of collateral damage of endocrine and exocrine function of pancreas and exploration of possible predictive biomarkers are warranted.

Conclusion

ICI-induced DM is a rare but potentially life-threatening adverse event, as DKA is often the first presentation. GADA positivity is related to an earlier onset of ICI-induced diabetes and a higher frequency of DKA development. Close monitoring of blood glucose in ICI application patients is essential. ICI-induced DM is usually insulin-dependent since the damage to β cells is irreversible, and immunotherapy rechallenge is feasible on the premise of well-controlled blood glucose. Further research on predictive biomarkers for the stratification of vulnerable patients is needed.

Authors' contributions

Minjiang Chen was the doctor in charge of the case we reported and helped with the follow-up of the patient. Jing Zhao and Wei Zhong assisted in the analysis of the results.

CRediT authorship contribution statement

Jia Liu: Formal analysis, Writing – original draft, Writing – review & editing. **Yuequan Shi:** Formal analysis, Writing – original draft, Writing – review & editing. **Xiaoyan Liu:** Formal analysis, Writing – review & editing. **Dongming Zhang:** Data curation, Writing – review & editing. **Haoran Zhang:** Data curation, Writing – review & editing. **Minjiang Chen:** . **Yan Xu:** Formal analysis, Writing – review & editing. **Jing Zhao:** . **Wei Zhong:** . **Mengzhao Wang:** Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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