Immune checkpoint inhibitor-associated diabetes mellitus in patients with HCC: Report of three cases and literature review

GAOCHENG WANG[1,2*], JINGJING WANG[3*], SHUILIN DONG[1], ZHANGUO ZHANG[1], WANGUANG ZHANG[1] and JIANPING ZHAO[1]

[1]Hepatic Surgery Center, Tongji Hospital; [2]The Second Clinical Department, Tongji Medical College; [3]Department of Medical Ultrasound, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430000, P.R. China

Received November 29, 2023; Accepted February 19, 2024

DOI: 10.3892/etm.2024.12486

Abstract. Treatment with immune checkpoint inhibitors (ICIs) is steadily becoming the standard of care for hepatocellular carcinoma (HCC), with an increasing number of immune-related adverse events (irAEs). However, only a small number of reports on the occurrence of diabetes mellitus (DM) in patients with HCC treated with ICIs have been published. In the present study, the clinical manifestations, laboratory findings, treatment and prognosis of three patients with advanced HCC were reported, who suffered immune-related DM when receiving treatment with ICIs. Furthermore, the relevant literature was reviewed in order to summarize clinical manifestations, possible mechanisms, diagnosis, prognosis of rechallenge and recommended management options, as well as clinical treatment suggestions. ICI-induced diabetes is rare but irAEs are potentially fatal, as diabetic ketoacidosis (DKA) is often the first manifestation. The incidence of immune-related DM is 0.86% and among those cases, the incidence of DKA is 59%. The combination of two ICIs markedly increases the risk. The human leukocyte antigen genotype, islet autoantibodies and autoreactive T cell-mediated β-cell destruction may be linked to the occurrence of immune-related DM. Patient education and clinicians' awareness of ICI-related DM are good management options. Adequate clinical judgment, close monitoring and early detection are also needed to decide whether to continue immunotherapy or to rechallenge it, so as to achieve the maximum benefit of clinical treatment.

Correspondence to: Dr Jianping Zhao, Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430000, P.R. China
E-mail: jpzhao@hust.edu.cn.zhe

*Contributed equally

Abbreviations: ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; irAE, immune-related adverse event; PD-1, programmed death-1; PD-L1, programmed death ligand-1; T1DM, type 1 diabetes mellitus; CNLC, China Liver Cancer; BCLC, Barcelona Clinic Liver Cancer; D-TACE, drug-eluting bead transarterial chemoembolization; PR, partial response; ICA, islet cell antibody; GADA, glutamic acid decarboxylase antibody; IAA, insulin autoantibody; IA-2A, protein tyrosine phosphatase autoantibody; ZnT8A, zinc transporter 8 autoantibody; CTLA-4, cytotoxic T lymphocyte associated antigen-4; HBV, chronic hepatitis B virus; ICI-DM, ICI-related DM; DKA, diabetic ketoacidosis; T3, triiodothyronine; T4, tetraiodothyronine; FPG, fasting plasma glucose

Key words: hepatocellular carcinoma, immune checkpoint inhibitor, immune-related adverse events, diabetes mellitus, diagnosis, management

Introduction

Primary liver cancer is currently the 4th most common malignant tumor and the 2nd leading cause of cancer-related death in China. Hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancers. Programmed death-1 (PD-1), programmed death ligand-1 (PD-L1) and other immune checkpoint inhibitors (ICIs) are used more extensively in cancer therapy by interfering with the immune checkpoint pathway to activate the immune system. However, PD-1 and PD-L1 are also widely expressed in normal tissue cells e.g. hematopoietic cells, pancreatic cells (1). Therefore, ICI therapy affects other tissue cells and has also caused a number of immune-related adverse events (irAEs), including a variety of endocrine disorders, such as thyroiditis, hypopituitarism and adrenal insufficiency (2). ICI-induced type 1 diabetes mellitus (T1DM) is an irAE with an incidence of 0.2-1.0% (3). A systematic review study demonstrated that in 172 ICI-induced DM (ICI-DM) cases, tumor types included melanoma (43.6%; 75/172), lung cancer (30.2%; 52/172), renal cell carcinoma (5.8%; 10/172), breast cancer (3.5%; 6/172), gastrointestinal cancers (3.5%; 6/172), lymphomas (2.9%; 5/172) and hepatocellular carcinoma (1.2%; 2/172) (4). Current research also suggests that the primary mechanism of ICI-induced T1DM is T-cell stimulation due to the loss of interaction between PD-1 and PD-L1 in pancreatic islets (5). A latest study reported the first case of a patient with HCC who developed fulminant T1DM and ketoacidosis during the therapeutic combination of atilizumab and bevacizumab (6). ICIs have been widely

used to treat HCC for a relatively short period of time and there is a lack of reports on the occurrence of DM in patients with HCC treated with ICIs. Therefore, information on such cases needs to be accumulated. The present study reported three cases of immune-associated DM after ICI treatment for HCC. Furthermore, the clinical attributes, epidemiology and primary mechanism of ICI-DM were reviewed, so as to draw attention of clinicians to this disease and, more importantly, its diagnosis and treatment.

Case presentation

Case 1. A 27-year-old female patient was admitted to Tongji Hospital (Wuhan, China) in January 2021 for detection of multiple tumors in the left lobe of the liver. The patient had a history of hepatitis B virus (HBV) infection >20 years and had never received any antiviral treatment. The patient did not have any complaints or discomfort and had no family or genetic history of HCC except HBV infection of the patient's mother. There was no positive sign such as hepatosplenomegaly or tenderness on physical examination. Blood routine and liver-renal function laboratory tests were normal but the biochemical examinations revealed an AFP level of 37,966 μg/l [normal range (NR), 0-15 μg/l], elevated (↑), and a protein induced by vitamin K absence (PIVKA-II) level of 5,834 mAU/ml (NR, 11.12-32.01 mAU/ml) ↑ (Table I). Furthermore, the MRI showed multiple tumors in the left lobe of the liver and a tumor embolus of the left branch of the portal vein was visible (Fig. 1). Therefore, the preliminary diagnosis was as follows: i) Chronic hepatitis B with compensated liver function and ii) primary HCC, China Liver Cancer (CNLC) stage IIIa/Barcelona Clinic Liver Cancer (BCLC) stage C (7). The patient received local treatment with drug-eluting bead transarterial chemoembolization (D-TACE) and systemic therapy with lenvatinib 8 mg/day and tislelizumab 200 mg/3 weeks, 21 days/cycle. After one month, the MRI showed that the patient had achieved a partial response (PR) (Fig. 1) according to the modified response evaluation criteria in solid tumors 1.1 (8) and a tumor biomarker decline. The patient then received 4 cycles of hepatic artery infusion chemotherapy (HAIC) and systemic therapy. The subsequent examination showed a complete response (Fig. 1) and the tumor biomarkers had declined to normal levels. The multidisciplinary team (MDT) refused surgery due to inadequate residual liver volume and recommended that the patient continued systemic therapy. However, after 6 months, contrast-enhanced ultrasonography and circulating tumor DNA (ctDNA) analysis (9) provided positive results, although the MRI still showed complete tumor necrosis. Furthermore, the residual liver volume was sufficient for operation due to left liver enlargement (Fig. S1), the liver function was Child-Pugh grade A (10) and the indocyanine green 15-min retention rate was 10.7% (11). Thus, right hemihepatectomy was performed and the pathological examination showed absence of viable cancer cells (Fig. 1). One month after the operation, as the ctDNA analysis turned to negative and no tumor recurrence was found in examinations including AFP, PIVKA-II and MRI, the patient continued the systemic therapy and received a routine examination where diabetes mellitus was excluded. In October 2022, the patient, who had by then received 88 weeks (cycle 30) of ICI therapy, was readmitted to Tongji Hospital (Wuhan, China) due to symptoms/complaints of nausea, vomiting, fever and lethargy. The patient's family denied a history of diabetes. The auxiliary examination revealed the following: Diabetes tests: Random plasma glucose 1,082 mg/dl (NR, 70.2-199.8 mg/dl) ↑, glycated hemoglobin (HbA1c) 9.8% (NR, 4-6%) ↑, fasting C-peptide 0.04 ng/ml (NR, 0.3-1.3 ng/ml) decreased (↓), urine glucose (3+) and urine ketone body (3+); electrolyte examination: Blood sodium 153.4 mmol/l (NR, 135-145 mmol/l) ↑, blood potassium 3.4 mmol/l (NR, 3.5-5.5 mmol/l) ↓, blood chlorine 107.5 mmol/l (NR, 98-106 mmol/l) ↑, effective plasma osmotic pressure 373.6 mOsm/l (NR, 280-310 mOsm/l) ↑; which suggested that the patient had diabetic ketoacidosis (DKA) and was in a hyperosmolar hyperglycemic state. Islet autoantibodies were as follows: Islet cell antibody (ICA) (+), glutamic acid decarboxylase antibody (GADA) (-), insulin autoantibody (IAA) (-), protein tyrosine phosphatase autoantibody (IA-2A) (-) and zinc transporter 8 autoantibody (ZnT8A) (-) (Table II). Thyroid function markers were as follows: Triiodothyronine (T3), 1.08 nmol/l (NR, 0.92-2.79 nmol/l); free triiodothyronine, 2.94 pmol/l (NR, 3.5-6.5 pmol/l); tetraiodothyronine (T4), 78.50 nmol/l (NR, 58.1-140.6 nmol/l); free thyroxine, 12.54 pmol/l (NR, 11.48-22.70 pmol/l); and thyroid-stimulating hormone, 24.34 μIU/ml (NR, 2-10 μIU/ml) ↑, which suggested that the patient had mild hypothyroidism. The diagnosis included the following: i) DKA, ii) hyperosmolar hyperglycemic state and iii) mild hypothyroidism. The patient was diagnosed with ICI-DM. After ketone correction and insulin pump therapy, the patient's ketone bodies turned negative and the patient's treatment was switched to 4 times of intensive insulin therapy with acceptable glycemic control. Approximately 2 months later, the patient continued the immunological treatment when blood glucose stability had been reached with insulin management. MRI suggested that there was no tumor recurrence until the final follow-up for the writing of this study in July 2023.

Case 2. A 56-year-old male patient was admitted to Tongji Hospital (Wuhan, China) in December 2022 for detection of multiple tumors in the right lobe of the liver. The patient had a history of HBV infection for 10 years and had not received any treatment. AFP and PIVKA-II were 5,834 μg/l ↑ and 25,243 mAU/ml ↑, respectively (Table I). The MRI showed multiple tumors in the right lobe of the liver and a tumor embolus of the right branch of the portal vein was visible (Fig. 1). The preliminary diagnosis was as follows: i) Chronic hepatitis B with compensated liver function and ii) primary HCC and CNLC IIIa/BCLC C. The patient received local treatment with HAIC and systemic therapy with lenvatinib 8 mg/day and tislelizumab 200 mg/3 weeks, 21 days/cycle. After 2 cycles, the MRI indicated that the patient achieved a PR with partial tumor necrosis (Fig. 1) and a tumor biomarker decline. At the same time, the patient complained of mild reactive cutaneous capillary endothelial proliferation, which was alleviated by application of steroid hormone cream without drug withdrawal. The patient then received the third treatment cycle. When the patient was admitted to Tongji Hospital (Wuhan, China) for the fourth treatment cycle, the routine examination indicated the following: Body mass index, 23.3 kg/m^2 (NR, 18.5-23.9 kg/m^2); diabetes

Table I. Clinicopathological characteristics of the patients.

Variable	Case 1	Case 2	Case 3
Age, years	27	56	67
Sex	Female	Male	Male
BMI, kg/m^2	20.4	23.3	25.7
Family history of DM	No	No	No
History of DM	No	No	No
Etiology of HCC	HBV	HBV	HBV
Cirrhosis	No	No	No
Child-Pugh	A	A	A
AFP, μg/l (NR, 0-15)	37966 ↑	5834 ↑	25342 ↑
PIVKA, mAU/ml (NR, 11.12-32.01)	422 ↑	ND	24245 ↑
Tumor size, cm	9.1	7.8	8.9
Tumor number, n	2	3	2
Portal vein tumor thrombus	Yes	Yes	No
Tumor differentiation	Moderate	Moderate	Well
BCLC stage	C	C	B
CNLC stage	IIIa	IIIa	IIa
Treatment regimen	Lenvatinib+tislelizumab	Apatinib+camrelizumab	Tislelizumab
Local treatment	D-TACE+HAIC	HAIC	D-TACE
Tumor response	Complete response	Partial response	Partial response
Operation	Yes	No	Yes

BMI, body mass index; DM, diabetes mellitus; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; PIVKA, protein in vitamin K absence; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; HBV, hepatitis B virus; D-TACE, drug-eluting bead transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; ND, not determined; NR, normal range; ↑, elevated.

tests: HbA1c, 7.7% ↑, blood glucose, 432 mg/dl ↑, C-peptide, 0.09 ng/ml ↓, urine glucose (2+) and urine ketone body (-), which suggested that the patient was in a hyperglycemic state. Electrolyte examination showed as following: Blood sodium, 131.4 mmol/l ↓; blood potassium, 4.5 mmol/l; blood chlorine, 104.4 mmol/l; and effective plasma osmotic pressure, 295.8 mOsm/l. Islet autoantibodies were as follows: GADA (+), ICA (-), IAA (-), IA-2A (-) and ZnT8A (-) (Table II). T3 and T4 levels were normal; thyroid autoantibodies were negative and no other endocrine system adverse reactions were found. The patient recovered one week after intensive treatment with an insulin pump. The patient achieved a stable level of blood glucose after two weeks and received low-dose rapid-acting insulin. The patient was diagnosed ICI-DM. Approximately 1.5 months later, the patient continued the immunological treatment and the latest MRI in July 2023 showed a PR.

Case 3. A 67-year-old male patient was admitted to Tongji Hospital (Wuhan, China) in July 2022 due to detection of a liver-occupying lesion in a routine health examination. The patient had a history of HBV infection for 30 years and received anti-HBV treatment for 10 years. The AFP and PIVKA-II were 25,342 μg/l ↑ and 24,245 mAU/ml ↑, respectively (Table I). The MRI showed two tumors in the right lobe of the liver and the maximum tumor diameter was 8.9 cm (Fig. 1). The preliminary diagnosis was as follows: i) Chronic hepatitis B with compensated liver function and ii) primary HCC, CNLC IIa/BCLC B. Surgery was rejected by the MDT due to high risk of recurrence and conversion therapy with D-TACE and tislelizumab was performed. One month later, the examination results showed a PR (Fig. 1) and significant tumor marker decline. The tumor situation of the patient was reassessed and discussed by the MDT and surgery was finally recommended. Right hemihepatectomy was successfully performed and the pathological examination showed tumor necrosis >80% (Fig. 1). One month after the operation, the patient continued Tislelizumad therapy for recurrence prevention. However, when the patient came to the outpatient department for routine follow-up examinations 2 months postoperatively and he had received 4 cycles of Tislelizumad therapy, the results showed the following: Diabetes tests: Blood glucose, 454 mg/dl ↑; HbA1c, 7.2% ↑; C-peptide, 0.08 ng/ml↓urine glucose (2+); urine ketone body (-), which showed that the patient was in a hyperglycemic state; electrolyte examination: Blood sodium 130.8 mmol/l ↓, blood potassium 4.8 mmol/l, blood chlorine 106.2 mmol/l ↑, effective plasma osmotic pressure 296.4 mOsm/l; and negativity for all islet autoantibodies (Table II). T3 and T4 levels were normal; thyroid autoantibodies were negative and no other endocrine system adverse reactions were found. With intensive treatment using the insulin pump, the blood glucose declined to normal levels and remained stable. The patient then received low-dose rapid-acting insulin. The patient was diagnosed ICI-DM. One month later, the patient continued immunological treatment and according to the latest MRI in July 2023, no tumor recurrence occurred.

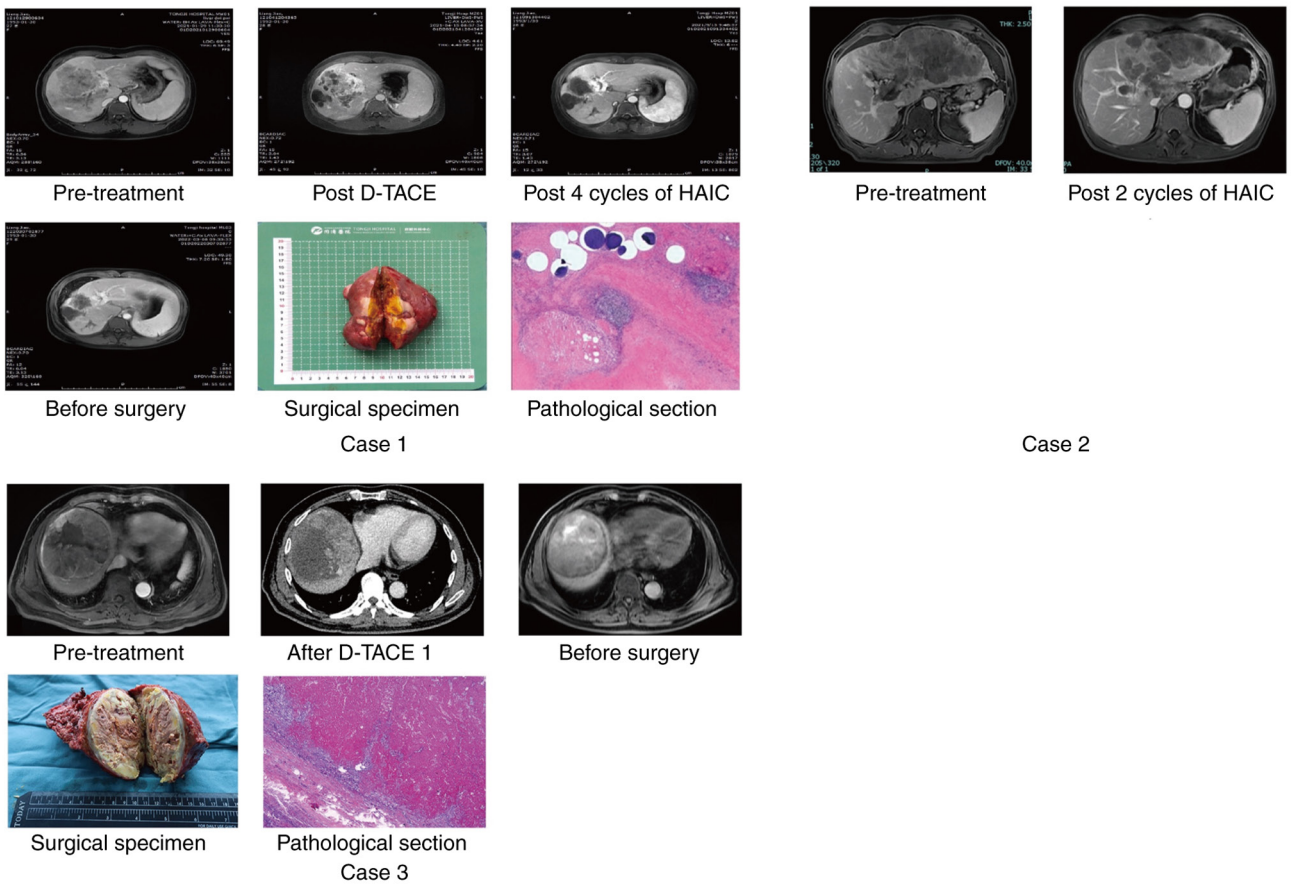

Figure 1. Treatment response of the three cases. Case 1, female, 27 years old; HCC with CNLC stage IIIa, multiple tumors in the left lobe of the liver and a tumor embolus of the left branch of the portal vein was visible; received 1 cycle of D-TACE and 4 cycles of HAIC with systemic therapy and achieved CR by mRECIST; received surgery and got pathological response of CR. Case 2, male, 56 years old; HCC with CNLC stage IIIa, multiple tumors in the right lobe of the liver and a tumor embolus of the right branch of the portal vein was visible; received 2 cycles of HAIC with systemic therapy and achieved PR by mRECIST. Case 3, male, 67 years old; HCC with CNLC stage IIa, two tumors in the right lobe of the liver and the maximum tumor diameter was 8.9 cm; received 1 cycle of D-TACE with systemic therapy and achieved PR by mRECIST; received surgery and got pathological response of tumor necrosis >80%. The pathological images was magnified 200 times. HCC, hepatocellular carcinoma; CNLC, China Liver Cancer; D-TACE, drug-eluting bead transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; PR, partial response; CR, complete response; mRECIST, modified response evaluation criteria in solid tumors.

Discussion

ICIs are significant in the history of cancer treatment. A review by Ribas and Wolchok (12) summarized that the objective response rate with ICI therapy in patients with Hodgkin's disease, skin melanoma, non-small cell lung cancer, renal cell carcinoma and HCC is 87, 35-40, 20, 25 and 20% respectively. In the tumor microenvironment, the PD-L1 expressed on tumor-associated macrophages, the PD-1 expressed during T and B lymphocyte activation and the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) expressed on T-regulatory cells, are all involved in regulating T-cell activity by T cell receptor signaling (13-15). ICIs such as anti-PD-1 and anti-PD-L1 inhibitors, can revitalize the anti-tumor function of immune cells by blocking the activation of inhibitory immune checkpoints, which, however, enhances the specific response from effector T cells to non-tumor tissues (16). The decrease of peripheral immune tolerance and increase of pro-inflammatory factor release when regulatory T cells are suppressed contribute to the development of irAEs (17). ICIs can cause toxic damage to numerous organs and systems, including the skin, gastrointestinal tract, musculoskeletal and oculus, the endocrine system, the nervous system, lung, kidney and the cardiovascular and hematologic systems (18). A systematic review showed that 14% of patients treated with PD-(L)1 inhibitor, 34% of patients treated with CTLA-4 inhibitors and 55% of patients on ICI combinations had irAEs (Grade ≥3) (19). Certain studies observed a negative impact of irAEs-related treatment discontinuation on survival. Naqash *et al* (20) found that patients with permanent ICI discontinuation due to irAEs had a 14 months shorter median overall survival compared to those who did not have permanent ICI discontinuation.

HCC is a typical inflammation-associated malignancy with a complex immune microenvironment (21). Chronic HBV infection and chronic hepatitis C virus infection create a tolerogenic immune microenvironment through T-cell exhaustion (loss of antiviral effector function of virus-specific $CD8^+$ T cells) and viral escape mutations (21,22). ICIs, including PD-1, PD-L1 and CTLA-4, have demonstrated significant therapeutic efficacy in the field of HCC treatment (23). The results of one study (CheckMate 040) showed that treatment with navulizumab significantly reduced tumors, with objective remission rates of 15-20% (24). Pembrolizumab showed similar results to those of navulizumab, with an overall remission rate of 14% (25). HCC is often combined with cirrhosis and systemic manifestations, and patients with extrahepatic organ dysfunction may exhibit

Table II. Laboratory test results at admission to hospital for DM.

Variable	Case 1	Case 2	Case 3
Number of ICI treatment cycles	35	6	12
Time of onset of ICI-DM, weeks	88	9	12
Other irAEs	Hypothyroidism	RCCEP	No
HbA1c, % (NR, 4-6)	9.8 ↑	7.7 ↑	7.2 ↑
Casual BG, mg/dl (NR, 70.2-199.8)	1082 ↑	432 ↑	454 ↑
C-peptide, ng/ml (NR, 0.3-1.3)	0.04 ↓	0.09 ↓	0.08 ↓
Na^+, mmol/l (NR, 135-145)	153.4 ↑	131.4↓	130.8↓
K^+, mmol/l (NR, 3.5-5.5)	3.4 ↓	4.5	4.8
Cl^+, mmol/l (NR, 98-106)	107.5 ↑	104.4	106.2 ↑
Diabetic ketoacidosis	Yes	No	No
GADA	-	+	-
ICA	+	-	-
IAA	-	-	-
IA-2A	-	-	-
ZnT8A	-	-	-
Continuation of ICIs	Yes	Yes	Yes
Tumor response after rechallenge	Stable disease	Partial response	Stable disease

DM, diabetes mellitus; ICI, immune checkpoint inhibitor; BG, blood glucose; irAEs, immune-related adverse events; GADA, glutamic acid decarboxylase antibody; ICA, islet cell antibody; IAA, insulin autoantibody; IA-2A, protein tyrosine phosphatase autoantibody; ZnT8A, zinc transporter 8 autoantibody; RCCEP, reactive cutaneous capillary endothelial proliferation; NR, normal range; ↑, elevated.

Table III. Differentiation among ICI-DM, T1DM and T2DM.

Variable	ICI-DM	T1DM	T2DM	(Refs.)
Age, median (IQR), years	63.6 (57.8-72.9)	37.1 (27.0-51.5)	63.8 (53.4-74.6)	(41)
HbA1c at first presentation, median (IQR), % (NR, 4-6)	10.1 (8.0-12.5) ↑	10.6(10.1-12.1) ↑	7.5 (6.3-10.1) ↑	(41)
Insulin dose, median (IQR), IU/kg/day	0.39 (0.35-0.50)	0.35 (0.21-0.52)	0.31 (0.18-0.51)	(41)
DKA at manifestation, %	26.7	0	0.4	(41)
Pancreatic autoantibodies, %	40.4(28)	90	NA	(28)
C-peptide levels, nmol/l (NR, 0.3-1.3)	<0.3 ↓ [63.4% (n=83)]	<0.3 ↓	Normal or excessive	(40)
Onset	Early or latent, or after the interruption of ICIs	Acute	Slow	(28)
Pancreatic enzymes	Mild increase	Lower lipase except in fulminant phenotype	NA	(28)

ICI, immune checkpoint inhibitor; ICI-DM, immune checkpoint inhibitor-associated diabetes mellitus; T1DM, type 1 DM; IQR, interquartile range; HbA1c, glycated hemoglobin; DKA, diabetic ketoacidosis; NA, not available.

signs and symptoms that overlap with irAEs or aggravate the severity of irAEs (2). Furthermore, irAEs leading to discontinuation of ICIs were also reported in 14.9% of HCC patients receiving immune-targeted therapy (n=327/2201, 95% CI: 13.4-16.4%), including fatigue (13.9%), diarrhea (10.2%), rash (10.0%), pruritus (9.9%) and decreased appetite (8.5%) (26). In addition, the probability of irAEs may be higher in patients with HCC receiving ICI combined therapy (27). Three cases reported had received lenvatinib and tislelizumab, apatinib and camrelizumab, and tislelizumab, respectively.

Similar to T1DM, ICI-DM is caused by endocrine toxicity due to ICI therapy. ICI-DM may cause lifelong persistent insulin deficiency, increase risks associated with diabetes complications and decrease life expectancy (28), indicating that ICI-DM should be emphasized in clinical practice. A previous study reported on T1DM caused by autoreactive T cell-mediated β-cell destruction (29). PD-1 and PD-L1 had inhibitory effects on pathogenic autoreactive $CD4^+$ T cell-mediated tissue destruction and effector cytokine production (1,30). PD-1 and PD-L1 deficiency accelerated the

onset and frequency of type I diabetes in non-obese diabetic mice (29,31). Lysogenic IFN-γCD8$^+$ T cells infiltrated pancreatic islets in islet sections from anti-PD-1-treated patients and IFN-γ activated the β-cell apoptotic pathway (32). *In vitro* experiments using human pancreatic islets from non-diabetic patients showed that IFN-γ promotes β-cell PD-L1 expression, which may act as a self-defense by expressing PD-L1 in response to IFN-γ (33). Therefore, blocking the PD-1/PD-L1 pathway in ICI-treated patients may contribute to the development of ICI-DM for aggravating the destruction of β-cells.

ICI-DM is a relatively rare but severe irAE with an incidence of 0.86% (261/30,337 patients) (34). Furthermore, 59% of patients with ICI-DM were complicated with DKA (35). The median age at the onset of ICI-DM was determined to be 61 years (36). The combination therapy resulted in an increased risk of immune-related DM compared to a single one (37). The mean time of onset of ICI-DM was 8.14 weeks (full range, 3.6-45 weeks) (38). One of the three patients reported in the present study had an onset of the disease at week 88 (cycle 30 of ICI treatment) and was accompanied with DKA. The other two patients developed ICI-DM at weeks 9 (cycle 3 of ICI treatment) and week 12 (cycle 4 of ICI treatment), respectively, and this was not accompanied with DKA. The clinical manifestations of ICI-DM are atypical and vary significantly among individuals, with mild cases showing only elevated blood glucose or severe cases showing acute onsets, rapid progression and even DKA (39). In case 1 of the present study, the patient presented with nausea, vomiting, fever and lethargy as symptoms of DKA, while the other two patients were diagnosed ICI-DM after laboratory tests during routine follow-up examinations. According to a previous study, 44.8% of ICI-DM cases had damage to other endocrine glands in addition to diabetes, including hypophysitis (5.2%) and thyroiditis (30.8%) (4). In case 1 of the present study, the pathology was accompanied by DKA and thyroiditis.

The diagnosis can be made if the patient's blood glucose is normal before the use of ICIs and one of the following three conditions is met after treatment: i) Typical diabetic symptoms (thirst, increased fluid intake, urination and weight loss caused by hyperglycemia) or acute metabolic disorders, such as itching of the skin and blurred vision, as well as random glucose ≥11.1 mmol/l; ii) fasting plasma glucose (FPG) ≥7.0 mmol/l; iii) 2-h blood glucose after 75 g glucose load ≥11.1 mmol/l (39). Furthermore, in the cases reported in the present study, C-peptide levels were 0.04, 0.09 and 0.08 nmol/l, respectively, which were <0.4 nmol/l in 91.6% of ICI-DM patients according to Wu *et al* (28). Table III provides certain differences and associations between ICI-DM and T1DM and T2DM (28,40,41), which is utilized to make differential diagnoses.

Currently, the human leukocyte antigen (HLA) genotype and islet autoantibodies are considered useful for early identification of patients who are more susceptible to ICI-DM. HLA-DR4 (a HLA serotype) showed the highest association with susceptibility to ICIs-DM (42). In a cohort study, 76% of patients with ICI-DM expressed HLA-DR4 (35). The patients in the present study did not undergo HLA genetic testing. Islet autoantibodies were considered a marker of T1DM and were detected in >90% of patients with T1DM in a previous study (43). de Filette *et al* (44) reported that at least one of the islet autoantibodies was positive in 53% of patients with TIDM and 15% of them had at least two positive autoantibodies. However, the association between islet autoantibodies and diagnosis of ICI-DM remains unclear (45). In the case series reported in the present study, ICA in case 1 was positive for DKA, while GADA was positive in case 2 and the patient from case 3 was negative for autoantibodies.

According to the Expert Consensus on Immune-related Adverse Reactions of the Endocrine System Caused by Immune Checkpoint Inhibitor (39), ICI-DM can be classified into 4 grades according to the severity of clinical symptoms and the level of FPG. According to this consensus, Case 1 may be classified as level 4 (FPG >27.8 mmol/l) and cases 2 and 3 are classified as level 3 (FPG is from 13.9 to 27.8 mmol/l). For grade 2 (FPG is from 8.9 to 13.9 mmol/l) and above, ICI treatment needs to be suspended until the blood glucose is controlled. Insulin therapy should be applied promptly for grade 3 and above, as well as for individuals with an acute increase in blood glucose or suspected ketosis. In the present case series, insulin therapy was used in all of the three patients when ICI-DM was diagnosed and the level of blood glucose was rapidly controlled under effective management. Furthermore, ICI treatment was suspended for all these three patients, which, however, was continued when blood glucose stability had been achieved with insulin management 1-2 months later. No severe irAEs were noted after the continuation of ICI treatment and no tumor recurrence or progression occurred.

In ICI-DM, β-cell damage was irreversible, patients required lifelong medication and steroids had no therapeutic effect on it (4). The main focus should be on the treatment with insulin injections and symptomatic supportive therapy (46). Blood glucose monitoring should be performed before each treatment cycle and every 3-6 weeks after the end of treatment (39). Patient education on early recognition of DM symptoms and DKA symptoms is also an important management option for ICI-DM (40). Ultimately, ICI rechallenge is feasible with good glycemic control (4).

In conclusion, ICI-DM is a rare but potentially fatal irAE, as DKA is often the first manifestation. Patient education and clinicians' awareness of adverse effects associated with ICIs are good management options. A thorough evaluation is needed to determine the likelihood of ICI-DM before starting ICI therapy, including the patient's general condition, history of previous immune disorders, laboratory tests and radiologic examinations. Blood glucose, C-peptide levels and HbA1c are practical screening options. At present, various therapeutic approaches combined with ICI therapy are gradually becoming the mainstream treatment for HCC and immunotherapy should not be easily abandoned because of potential irAEs. Adequate clinical judgment, close monitoring and early detection of irAEs are needed to decide whether to continue immunotherapy or to rechallenge it according to the combination of grading and patient condition, which aims to achieve the maximum benefit of clinical treatment.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 82003403).

Availability of data and materials

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

Authors' contributions

Conception and design of the study: GW and JZ. Acquisition of data: JW and SD. Collection of relevant articles: ZZ and WZ. Data analysis, drafting of manuscript and critical revision: GW. ZZ and WZ checked and confirm the authenticity of the raw data. All authors contributed to the article and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Board of Tongji Hospital (Wuhan, China; approval no. TJ-IRB20210935). Written informed consent for clinical research on the data generated during therapy was obtained from all enrolled patients.

Patient consent for publication

Written consent for the publication of potentially identifiable patient/clinical data and/or images was obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

References

1. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, Koulmanda M, Freeman GJ, Sayegh MH and Sharpe AH: Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med 203: 883-895, 2006.
2. Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, Shen C, Duma N, Vera Aguilera J, Chintakuntlawar A, *et al*: Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: A systematic review and meta-analysis. JAMA Oncol 5: 1008-1019, 2019.
3. Wright JJ, Salem JE, Johnson DB, Lebrun-Vignes B, Stamatouli A, Thomas JW, Herold KC, Moslehi J and Powers AC: Increased reporting of immune checkpoint inhibitor-associated diabetes. Diabetes Care 41: e150-e151, 2018.
4. Liu J, Shi Y, Liu X, Zhang D, Zhang H, Chen M, Xu Y, Zhao J, Zhong W and Wang M: Clinical characteristics and outcomes of immune checkpoint inhibitor-induced diabetes mellitus. Transl Oncol 24: 101473, 2022.
5. Cho YK and Jung CH: Immune-checkpoint inhibitors-induced type 1 diabetes mellitus: From Its molecular mechanisms to clinical practice. Diabetes Metab J 47: 757-766, 2023.
6. Ikeda M, Tamada T, Takebayashi R, Okuno G, Yagura I, Nakamori S, Matsumura T, Yoshioka T, Kaneko S and Kanda N: Development of fulminant type 1 diabetes mellitus in the course of treatment with atezolizumab for hepatocellular carcinoma. Intern Med 62: 1775-1779, 2023.
7. Xie DY, Ren ZG, Zhou J, Fan J and Gao Q: 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: Updates and insights. Hepatobiliary Surg Nutr 9: 452-463, 2020.
8. Lee JS, Choi HJ, Kim BK, Park JY, Kim DY, Ahn SH, Han KH, Baek SE, Chung YE, Park MS, *et al*: The modified response evaluation criteria in solid tumors (RECIST) yield a more accurate prognoses than the RECIST 1.1 in hepatocellular carcinoma treated with transarterial radioembolization. Gut Liver 14: 765-774, 2020.
9. Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, Italiano A, Lindberg J, Merker JD, Montagut C, *et al*: ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO precision medicine working group. Ann Oncol 33: 750-768, 2022.
10. Peng Y, Qi X and Guo X: Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: A systematic review and meta-analysis of observational studies. Medicine (Baltimore) 95: e2877, 2016.
11. Le Roy B, Grégoire E, Cossé C, Serji B, Golse N, Adam R, Cherqui D, Mabrut JY, Le Treut YP and Vibert E: Indocyanine green retention rates at 15 min predicted hepatic decompensation in a western population. World J Surg 42: 2570-2578, 2018.
12. Ribas A and Wolchok JD: Cancer immunotherapy using checkpoint blockade. Science 359: 1350-1355, 2018.
13. Park DJ, Sung PS, Lee GW, Cho S, Kim SM, Kang BY, Hur W, Yang H, Lee SK, Lee SH, *et al*: Preferential expression of programmed death ligand 1 protein in tumor-associated macrophages and its potential role in immunotherapy for hepatocellular carcinoma. Int J Mol Sci 22: 4710, 2021.
14. Wei SC, Duffy CR and Allison JP: Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 8: 1069-1086, 2018.
15. Rowshanravan B, Halliday N and Sansom DM: CTLA-4: A moving target in immunotherapy. Blood 131: 58-67, 2018.
16. He X and Xu C: Immune checkpoint signaling and cancer immunotherapy. Cell Res 30: 660-669, 2020.
17. Passat T, Touchefeu Y, Gervois N, Jarry A, Bossard C and Bennouna J: Physiopathological mechanisms of immune-related adverse events induced by anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies in cancer treatment. Bull Cancer 105: 1033-1041, 2018 (In French).
18. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, Gerber DE, Hamad L, Hansen E, Johnson DB, *et al*: Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 9: e002435, 2021.
19. Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S and Péron J: A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer 145: 639-648, 2019.
20. Naqash AR, Ricciuti B, Owen DH, Florou V, Toi Y, Cherry C, Hafiz M, De Giglio A, Muzaffar M, Patel SH, *et al*: Outcomes associated with immune-related adverse events in metastatic non-small cell lung cancer treated with nivolumab: A pooled exploratory analysis from a global cohort. Cancer Immunol Immunother 69: 1177-1187, 2020.
21. Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, Pikarsky E, Zhu AX and Finn RS: Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 19: 151-172, 2022.
22. Zhang CY, Liu S and Yang M: Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy. World J Gastroenterol 28: 3346-3358, 2022.
23. Callahan MK, Postow MA and Wolchok JD: Targeting T cell co-receptors for cancer therapy. Immunity 44: 1069-1078, 2016.
24. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, *et al*: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389: 2492-2502, 2017.
25. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, *et al*: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 19: 940-952, 2018.
26. Ziogas IA, Evangeliou AP, Giannis D, Hayat MH, Mylonas KS, Tohme S, Geller DA, Elias N, Goyal L and Tsoulfas G: The role of immunotherapy in hepatocellular carcinoma: A systematic review and pooled analysis of 2,402 patients. Oncologist 26: e1036-e1049, 2021.

27. Nikoo M, Hassan ZF, Mardasi M, Rostamnezhad E, Roozbahani F, Rahimi S and Mohammadi J: Hepatocellular carcinoma (HCC) immunotherapy by anti-PD-1 monoclonal antibodies: A rapidly evolving strategy. Pathol Res Pract 247: 154473, 2023.
28. Wu L, Tsang V, Menzies AM, Sasson SC, Carlino MS, Brown DA, Clifton-Bligh R and Gunton JE: Risk factors and characteristics of checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM): A systematic review and delineation from type 1 diabetes. Diabetes Care 46: 1292-1299, 2023.
29. Francisco LM, Sage PT and Sharpe AH: The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 236: 219-242, 2010.
30. Fujisawa R, Haseda F, Tsutsumi C, Hiromine Y, Noso S, Kawabata Y, Mitsui S, Terasaki J, Ikegami H, Imagawa A and Hanafusa T: Low programmed cell death-1 (PD-1) expression in peripheral CD4(+) T cells in Japanese patients with autoimmune type 1 diabetes. Clin Exp Immunol 180: 452-457, 2015.
31. Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T and Honjo T: Establishment of NOD-Pdcd1-/- mice as an efficient animal model of type I diabetes. Proc Natl Acad Sci USA 102: 11823-11828, 2005.
32. Perdigoto AL, Deng S, Du KC, Kuchroo M, Burkhardt DB, Tong A, Israel G, Robert ME, Weisberg SP, Kirkiles-Smith N, *et al*: Immune cells and their inflammatory mediators modify β cells and cause checkpoint inhibitor-induced diabetes. JCI Insight 7: e156330, 2022.
33. Osum KC, Burrack AL, Martinov T, Sahli NL, Mitchell JS, Tucker CG, Pauken KE, Papas K, Appakalai B, Spanier JA and Fife BT: Interferon-gamma drives programmed death-ligand 1 expression on islet β cells to limit T cell function during autoimmune diabetes. Sci Rep 8: 8295, 2018.
34. Chen X, Affinati AH, Lee Y, Turcu AF, Henry NL, Schiopu E, Qin A, Othus M, Clauw D, Ramnath N and Zhao L: Immune checkpoint inhibitors and risk of type 1 diabetes. Diabetes Care 45: 1170-1176, 2022.
35. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, Gettinger S, Sznol M, Young A, Rushakoff R, *et al*: Collateral damage: Insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes 67: 1471-1480, 2018.
36. Zhang Z, Sharma R, Hamad L, Riebandt G and Attwood K: Incidence of diabetes mellitus in patients treated with immune checkpoint inhibitors (ICI) therapy-A comprehensive cancer center experience. Diabetes Res Clin Pract 202: 110776, 2023.
37. Lou S, Cao Z, Chi W, Wang X, Feng M, Lin L, Ding Y, Liu K, Qu L, Zhao G, *et al*: The safety concerns regarding immune checkpoint inhibitors in liver cancer patients rising mainly from CHB. Front Pharmacol 14: 1164309, 2023.
38. Rodríguez de Vera-Gómez P, Piñar-Gutiérrez A, Guerrero-Vázquez R, Bellido V, Morales-Portillo C, Sancho-Márquez MP, Espejo-García P, Gros-Herguido N, López-Gallardo G, Martínez-Brocca MA and Soto-Moreno A: Flash glucose monitoring and diabetes mellitus induced by immune checkpoint inhibitors: An approach to clinical practice. J Diabetes Res 2022: 4508633, 2022.
39. Immune-endocrinology Group, Chinese society of Endocrinology, Chinese Medical Association: Chinese expert consensus on immune checkpoint inhibitors-induced endocrine immune-related adverse events (2020). Chin J Endocrinol Metab 37: 1-16, 2021 (In Chinese).
40. Lo Preiato V, Salvagni S, Ricci C, Ardizzoni A, Pagotto U and Pelusi C: Diabetes mellitus induced by immune checkpoint inhibitors: Type 1 diabetes variant or new clinical entity? Review of the literature. Rev Endocr Metab Disord 22: 337-349, 2021.
41. Tittel SR, Laubner K, Schmid SM, Kress S, Merger S, Karges W, Wosch FJ, Altmeier M, Pavel M and Holl RW; DPV Initiative: Immune-checkpoint inhibitor-associated diabetes compared to other diabetes types-A prospective, matched control study. J Diabetes 13: 1007-1014, 2021.
42. Lin C, Li X, Qiu Y, Chen Z and Liu J: PD-1 inhibitor-associated type 1 diabetes: A case report and systematic review. Front Public Health 10: 885001, 2022.
43. American Diabetes Association: 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2020. Diabetes Care 43 (Suppl 1): S14-S31, 2020.
44. de Filette JMK, Pen JJ, Decoster L, Vissers T, Bravenboer B, Van der Auwera BJ, Gorus FK, Roep BO, Aspeslagh S, Neyns B, *et al*: Immune checkpoint inhibitors and type 1 diabetes mellitus: A case report and systematic review. Eur J Endocrinol 181: 363-374, 2019.
45. Deligiorgi MV and Trafalis DT: A concerted vision to advance the knowledge of diabetes mellitus related to immune checkpoint inhibitors. Int J Mol Sci 24: 7630, 2023.
46. Clotman K, Janssens K, Specenier P, Weets I and De Block CEM: Programmed cell death-1 inhibitor-induced type 1 diabetes mellitus. J Clin Endocrinol Metab 103: 3144-3154, 2018.

Copyright © 2024 Wang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.