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CASE REPORT

Sintilimab-induced autoimmune diabetes: A case report and review of the literature

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Abstract

BACKGROUND

With the widespread application of immune checkpoint inhibitor (ICI) therapy, the number of immune-related adverse effects (irAEs) has increased over the years. Autoimmune diabetes mellitus (DM) is a rare irAEs of ICIs and can be troublesome and life threatening.

CASE SUMMARY

We report a 78-year-old woman with no history of diabetes who presented with hyperglycemia up to 23.4 mmol/L (random blood glucose level) after 14 courses of sintilimab. Hemoglobin A1c was 8.2%, fasting insulin was 0.29 mIU/mL, and fasting C-peptide was decreased to a level with negative autoantibodies. Combing her medical history and laboratory examination, she was diagnosed with programmed cell death (PD)-1-inhibitor-induced, new-onset autoimmune DM. After controlling her blood glucose, she was treated with daily insulin by subcutaneous injection. She was allowed to continue anti-PD-1 therapy and she still obtained some therapeutic efficacy. We also reviewed some published cases (n = 36) of PD-1/PD-ligand 1 (PD-L1) inhibitor-induced DM. We also discuss potential pathogenic mechanisms, clinical features, prognostic markers (β cell antibodies, human leukocyte antigen type, PD-L1 Level) of this rare adverse effect.

CONCLUSION

It is important for all clinicians to be aware of DM as an irAEs of ICIs.

Key Words: Sintilimab; Immune related adverse effects; Small cell lung cancer; Autoim-

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Core tip: We report a case of programmed cell death (PD)-1-inhibitor-induced autoimmune diabetes mellitus (DM) after treatment of small cell lung cancer, and reviewed some published cases (n = 36) of PD-1/PD-ligand 1 inhibitor-induced DM. Plasma glucose monitoring is significant for preventing the occurrence of diabetic ketoacidosis.

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been used widely in the treatment of various advanced malignances. Programmed cell death (PD)-1 (also known as CD279) is one of the best-known ICs, and is expressed on T cells, B cells, activated monocytes, dendritic cells (DCs) and natural killer cells[1]. Its ligand PD-L1 (B7-H1, CD274) is expressed on antigen-presenting cells, macrophagocytes, nonhematopoietic cells and parenchymatous organs such as heart, lungs, placenta and liver. When PD-1 binds to PD-L1 (B7-H1, CD274)/PD-L2 (B7-DC, CD273), a signal that inhibits the proinflammatory ability of T cells and attenuates the function of cytotoxic T cells is delivered. T cell tolerance protects human tissues from immune-mediated tissue damage[2]. However, PD-1 and PD-L1 pathways are also seized by tumors, which impairs tumor immunity and facilitates tumor survival. PD-1/PD-L1 inhibitors remove the inhibitory signals of T cells, enhance cytotoxicity and increase cytokine production. Thus, ICIs can enhance the antitumor effect, but they also increase the chance of inflammatory injury (Figure 1).

According to recent research, ICIs induce immune-related adverse events (irAEs) that involve the whole body, including skin (46%–62%), gastrointestinal tract (22%–48%), autoimmune hepatitis (7%–33%), endocrine system (12%–34%), respiratory system (3%–8%) and urinary system (1%–7%)[3]. PD-1/PD-L1-inhibitor-associated autoimmune diabetes mellitus (DM) is rare, with an incidence rate of 0.1% in clinical trials[4]. ICI-induced DM (ICI-DM) is an irreversible event that can be life-threatening if not promptly recognized. Its incidence has increased with the widespread use of immunotherapy. Therefore, it is important for clinicians to fully understand the pathogenic mechanisms of these treatments and their potential irAEs.

Sintilimab is a PD-1 inhibitor that was newly approved in China for treatment of relapsed or refractory Hodgkin's lymphoma in February 2019[5], and it is now also a feasible treatment for a variety of solid tumors, including non-small cell lung cancer and esophageal cancer. Small cell lung cancer (SCLC) is a malignant tumor with rapid metastasis and poor prognosis. Treatment of SCLC with sintilimab alone or combined with other chemotherapeutic drugs is rare and there are no reports published to describe its clinical effects. Here, we present the first case of new-onset autoimmune DM in a patient with SCLC during treatment with sintilimab, along with marked antitumor efficacy. We also provide a review of case reports of ICI-DM.

This study was conducted according to the advice of the Ethics Center of Zhejiang Provincial People's Hospital. The patient's written informed consent was obtained for publication of this case and any images or information that may identify the patient.

CASE PRESENTATION

Chief complaints

A 78-year-old Chinese woman was diagnosed with SCLC 1 year ago with no history of DM who presented with hyperglycemia up to 23.4 mmol/L (random blood glucose

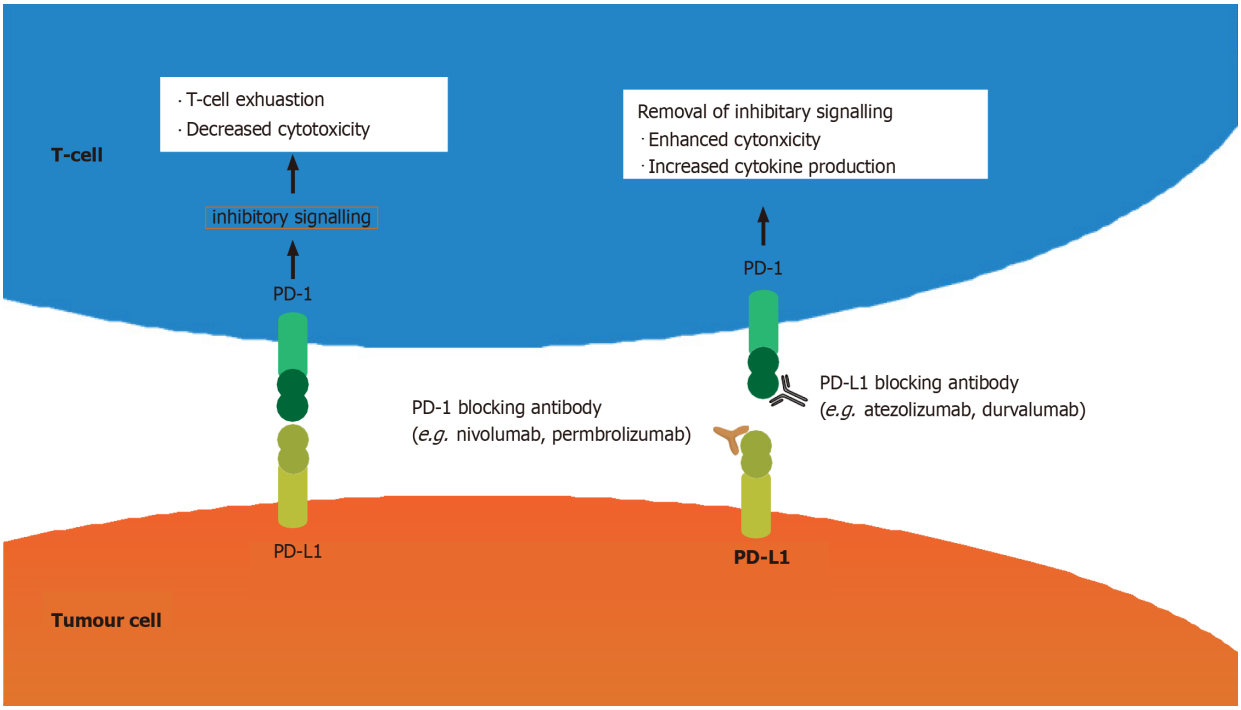

Figure 1 Mechanism of action of PD-1/PD-L1 immune checkpoint inhibitors. PD-1: Programmed death-1; PD-L1: Programmed death-ligand 1.

level) after 14 courses of sintilimab. The plasma glucose line shown in Figure 2.

History of present illness

The patient initially developed polyuria and polydipsia and her blood glucose level showed a mild increase after 12 cycles of sintilimab, but the treatment was continued. Two months later, the patient presented with hyperglycemia up to 23.4 mmol/L (random blood glucose level) with strong positive uric sugar (++++) and hemoglobin A1c of 8.2%.

History of past illness

The patient was diagnosed with SCLC on October 29, 2019 in the First Affiliated Hospital of Zhejiang University. She underwent endobronchial ultrasound-guided transbronchial needle aspiration, and the results were suggestive of poorly differentiated cell carcinoma, considered to be SCLC. Immunohistochemical staining demonstrated CKpan(+), P40(), P63(+), Ki67 (50%+), TTF-1(+), CgA(+), Syn(+), CD56(+) and CD45(). The patient immediately underwent concurrent chemotherapy and immunotherapy for SCLC (extensive). She received her first treatment, etoposide 82 mg, days 1–3; cisplatin 20 mg, days 1–3; and sintilimab 200 mg, day 1; EP plan) on October 30, 2019. The patient came to our hospital to continue treatment. After we assessed her condition, she continued the EP treatment plan, but we reformulated the doses as follows: etoposide 240 mg, days 1–3; cisplatin 250 mg, days 1–3; and sintilimab 200 mg, day 1. This therapy did control her disease well, with decreased tumor markers and no metastases found on imaging. In the following days, she came to our hospital monthly for evaluation. Her blood glucose level was normal after treatment. After five cycles with the EP plan, we changed to sintilimab 200 mg and anlotinib 8 mg q.d. because of severe gastrointestinal adverse reactions. After three cycles of the new treatment, the patient developed lower urinary tract infection, such as urinary frequency, difficulty urinating, pain with urination, and hematuria. Therefore, we had to stop anlotinib and used levofloxacin to treat the infection. Hence, we used sintilimab monotherapy, and imaging showed good antitumor effects (Figure 2). During the treatment, the patient only had mild gastrointestinal symptoms such as nausea and poor appetite.

Personal and family history

The patient denied any other specific personal history. But she has family history of cancer, her grandmother died of lung cancer, whereas her father died of colorectal cancer.

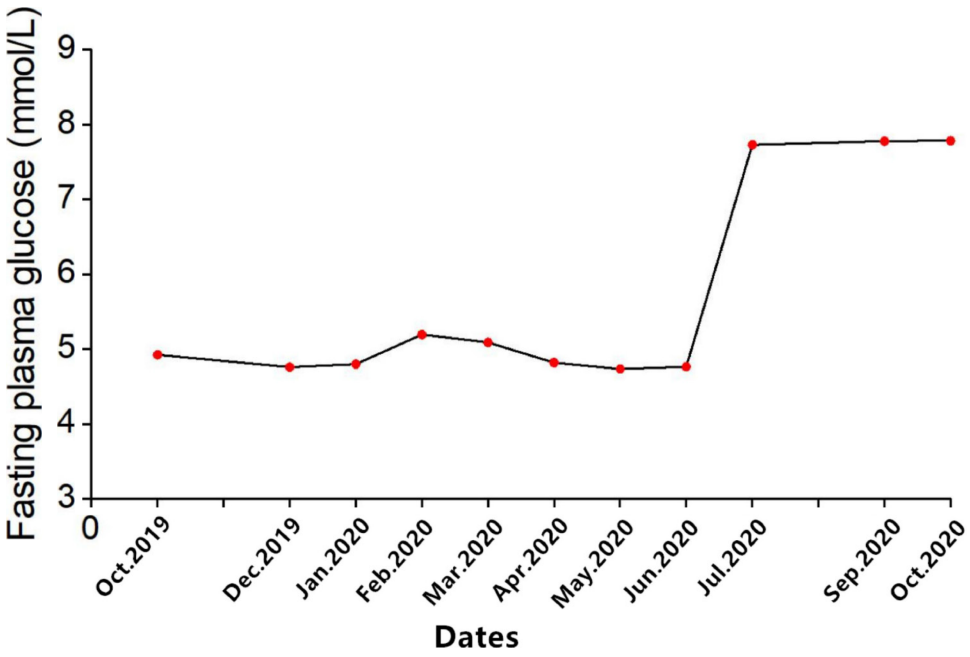

Figure 2 Changes of fasting plasma glucose level after initiation of sintilimab.

Physical examination

Height: 151 cm; weight: 40.4 kg; body mass index: 17.71 kg/m^2. Physical examination was no positive signs.

Laboratory examinations

Other laboratory evaluation (Table 1) showed that urinary ketones were negative and blood pH was normal and the hypothalamic–pituitary–gonadal axis and hypothalamic–pituitary–adrenocortical axis were negative; but antithyroid autoantibodies were 17.80 IU/mL (normal< 4.0 IU/mL) and antithyroid peroxidase autoantibodies were 10.0 IU/mL (normal < 9.0 IU/mL). The islets antibodies tests were all negative, including anti-glutamic acid decarboxylase 65 (GADA) antibody, anti-islet cell antibody, and anti-insulin antibody tests were all negative. Moreover, zinc transporter 8 antibody levels were unavailable in our hospital. Human leukocyte antigen (HLA) class I and II, which was shown in Table 2, including HLA-A, B, C, DRB1, DQB1 and DPB1, were tested by polymerase chain reaction-sequence based typing (PCR-SBT).

Imaging examinations

According to the computed tomography scanning of the patient's chest (Figure 3B), the tumor was shrinking, which indicated that anti-PD-1 therapy was effective.

FINAL DIAGNOSIS

The patient had no history of DM or autoimmune disease before treatment, and there was no medication, infection, thromboembolic event, or other factor that could cause hyperglycemia; according to the laboratory evaluation, thus, sintilimab-induced, new-onset autoimmune DM was diagnosed.

TREATMENT

Intravenous fluid infusion, continuous subcutaneous insulin infusion (insulin infusion pump therapy) and other supportive treatments were administered. After 10 d of insulin infusion pump therapy, the patient's plasma glucose returned to normal levels. We performed a simple oral glucose tolerance test that revealed that the fasting and 0–2-h insulin levels were 0.29 and 2.50 IU/mL; fasting and 0–2-h C-peptide levels were 0.22 and 0.52 ng/mL, which indicated an insufficient function of pancreatic islet β

Table 1 Laboratory data at presentation

Admission bloods (normal range, units)	Results
BMI (kg/m^2)	18.8
Finger prick glucose (mmol/L)	23.4
urinary glucose	++++
Ketones (mmol/L)	Negative
HbA1c [4%–6% (20–42 mmol/mol)]	8.2%
C-peptide (1.0–7.1 ng/mL)	0.22
Testosterone (0.1–1.1 ng/mL)	0.18
Progesterone (0.00–0.20 ng/mL)	< 1.0
Estradiol (10.00–28.00 pg/mL)	< 10
FSH (26.70–133.40 IU/L)	45.52
LH (5.20–62.0 IU/L)	18.55
Prolactin (5.20–26.50 ng/mL)	9.13
8 am ACTH (0.00-46.00 pg/mL)	15.90
8 am cortisol (67.00-226.00 μg/L)	113.00
ARR (≤ 150 pg/mL)	2.53
TSH (15.00–65.00 mIU/L)	0.98
TT3 (0.66–1.61ug/L)	1.03
TT4 (54.40–118.50 ug/L)	116.86
FT3 (1.0–7.1 ng/L)	3.35
FT4 (1.0–7.1 ng/L)	6.00
ATG (<4.00 IU/L)	17.80
TPO (<9.00 IU/L)	10.00
GAD	Negative
ICA	Negative
IAA	Negative
ZnT8	Negative
IL-2 (0.00–4.10 pg/mL)	0.04
IL-4 (0.10-3.20 pg/mL)	0.01
IL-6 (0.00–5.00 pg/mL)	0.00
IL-10 (0.00–5.90 pg/mL	0.13
TNF-α (0.00–6.00 pg/mL)	0.81
IFN-γ (0.00–6.00 pg/mL	1.36
IL-17A (0.00–5.90 pg/mL)	0.70

BMI: Body mass index; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; FT3: Free triiodothyronine; TT4: Total thyroxine; TT3: Total triiodothyronine; PTH: Parathyroid hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ACTH: Adrenocorticotropic hormone; HGH: Human growth hormone; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma; ATG: Anti-thyroglobulin antibodies; TPO: Thyroid peroxidases antibody; GAD: Anti-glutamic acid decarboxylase 65; ICA: Anti-islet cell antibody; IAA: Anti-insulin antibody; ZnT8: Zinc transporter8 antibody; ARR: Aldosterone/renin ratio.

cells. Subsequently, she was switched to once-daily basal insulin detemir (long-acting insulin, 10 U) plus thrice-daily premeal insulin aspart (fast acting insulin, 11 U, respectively 3U, 4U, 3U three meals) subcutaneous injection for long-term treatment.

Table 2 High-resolution genotyping of human leukocyte antigen class I and II of patient with diabetes induced by immune checkpoint inhibitor

HLA type	A	B	C	DRB1	DQB1	DPB1
Alleles	02:01	35:03	04:01	04:01	03:01	02:01
	24:02	51:05	14:02	14:03	03:02	02:01

HLA: Human leukocyte antigen.

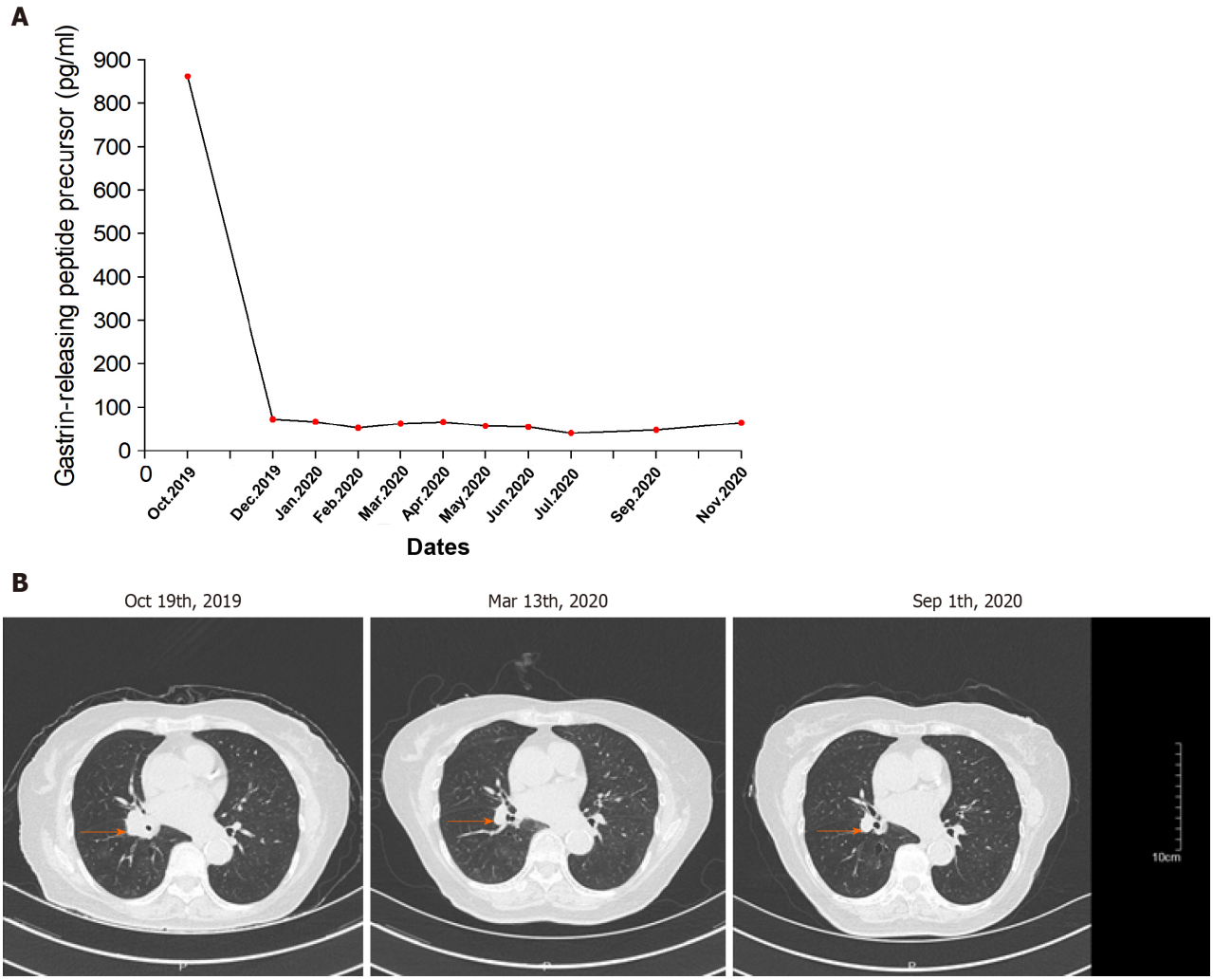

Figure 3 Course of treatment of patients with diabetes induced by immune checkpoint inhibitors. A: Changes of gastrin-releasing peptide precursor level during each period; B: Contrast-enhanced chest computed tomography during each period. Red arrows indicate the tumors.

OUTCOME AND FOLLOW-UP

By the time the manuscript was completed, the patient was without evidence of SCLC recurrence with no further treatment since sintilimab (Figure 3). Other endocrine adverse effects such as thyroiditis and hypophysitis did not occur. We retrieved 36 relevant case reports from 2016 to 2020 in PubMed to determine the common features of ICI-DM (Table 3)[6-37]. Table 4 summarizes the key features.

DISCUSSION

Sintilimab is a fully humanized IgG4 monoclonal antibody that binds to PD-1, then interferes with the interaction of PD-1 and its ligands (PD-L1 and PD-L2), thus

Table 3 Reported cases of diabetes induced by immune checkpoint inhibitors

Ref.	Sex/ Age (yr)	Primary diagnosis	Relevant history	Anti-PD-1/Anti-PD-L1 drug	Other chemo-therapies	Presentation	Other side effects	HbA1c	C peptide	Antibodies	Time with anti-PD-1 (w)	HLA
Araújo *et al*[6], 2017	F/73	NSCLC	N	Nivolumab	Carboplatin +pemetrexed	DKA	N	7.20%	0.06 ng/ml	GAD+	5	High risk: DR3-DQ2/DR4-DQ8
Li *et al*[7], 2020	M/73	NSCLC	N	Nivolumab	Sunitinib	DKA	N	10.90%	0.24 ng/mL	-	30	Unavailable
Abdullah *et al*[8], 2019	M/68	Melanoma	N	Nivolumab	None	DKA	N	Unavailable	0.1 ng/mL	-	4	Unavailable
Kapke *et al*[9], 2017	M/83	Oral squamous cell carcinoma	Hypothyroidism	Nivolumab	None	DKA	N	Unavailable	0.32 ng/mL	GAD+	12	High risk: DRB1*08, DRB1*11, DQB1*03, DQB1*04, DQA1*04, and DQA1*05.
Kapke *et al*[9], 2017	F/63	Urothelial carcinoma of the bladder	Hypothyroidism	Atezolizumab	Gemcitabine + cisplatin	DKA	N	Unavailable	0.02 ng/mL	GAD+	6	High risk: DRB1*03, DRB1*04, DQB1*02, DQB1*03,DQA1*03, and DQA1*05.
Lowe *et al*[10], 2016	M/54	Melanoma	N	Nivolumab +ipilimumab	None	DKA	Autoimmune, thyroiditis	Unavailable	< 0.1 ng /mL	GAD+	19	Unavailable
Rahman *et al*[11], 2020	M/64	Renal cell carcinoma	T2DM	Atezolizumab	Bevacizumab	DKA	N	Unavailable	Unavailable	GAD+	12	Unavailable
Mengíbar *et al*[12], 2019	M/55	Urothelial carcinoma of the bladder	Family history of T1D	Durvalumab	None	DKA	Hypothyroidism	8.40%	0.02 ng/mL	GAD+, IA2+	3	Unavailable
Kichloo *et al*[13], 2020	F/77	Colonic adenocarcinoma	N	Pembrolizumab	FOLFOX (leucovorin, fluorouracil, oxaliplatin	DKA	N	8.80%	Unavailable	-	44	Unavailable
Delasos *et al*[14], 2020	M/77	Neuroendocrine tumor	N	Nivolumab	Carboplatin + etoposide	DKA	N	8.30%	Unavailable	-	28	Unavailable
Hickmott *et al*[15], 2017	M/57	Urothelial cancer	N	Atezolizumab	Cisplatin + gemcitabine	DKA	N	7.50%	0.65 ng/mL	-	15	High risk: DRB1*11, DRB1*04; DRB3*02; DRB4*01; DQB1*03, DQB1*03
Sothornwit *et al*[16], 2017	F/52	NSCLC	N	Atezolizumab	None	DKA	Transaminitis	7.90%	0.1 ng/ml	GAD+	24	DRB1 03, DRB1 14, DQB1 02, DQB1 05 (DR3-

												DQ2/DR14-DQ5)
Changizzadeh *et al* [17], 2019	M/44	Melanoma	N	Nivolumab + ipilimumab	None	DKA	N	6.50%	Unavailable	-	12	Unavailable
Gunawan *et al*[18], 2018	M/52	Melanoma	N	Nivolumab + ipilimumab	None	hyperglycemia Ketonuria	Hypophysitis, thyroiditis, adrenal inefficiency	7.70%	0.05 nmol/L (0.016 ng/ml)	-	3	Unavailable
Gunjur *et al*[19], 2019	F/77	Melanoma	N	Pembrolizumab	None	DKA	Thyroidits	6.9% (normal range: <6.5%)	0.07 ng/ml	GAD+,IA2+	3	DRB1*04:16, DQB1*02:05 and DQA1*01:03
Atkins *et al*[20], 2018	M/50	Squamous cell carcinoma of the tonsil	N	Avelumab	Utomilumab	DKA	N	6.40%	63 pmol/L	GAD+	4	Unavailable
Marchand *et al*[21], 2019	F/65	Melanoma	N	Nivolumab + ipilimumab	None	DKA	Hypereosinophilia	7.30%	<0.1 ng/mL	-	12	DRB1*01:01 DQA1*01DQB1*03:01 DRB1*11:01 DQA1*05 DQB1*05:01
Tzoulis *et al*[22], 2018	F/56	NSCLC	N	Nivolumab	Pemetrexed + cisplatin	DKA	N	8.20%	Undetectable	GAD+	7	Unavailable
Porntharukchareon *et al*[23], 2020	M/70	NSCLC	N	Pembrolizumab + ipilimumab	None	DKA	IAD	6.50%	< 0.1 ng/ml	-	14	Unavailable
Lee *et al*[24], 2020	M/67	NSCLC	T2DM	Nivolumab	Carboplatin + paclitaxel	DKA	Thyroiditis	7.60%	<0.1 ng/mL	GAD+	2	Unavailable
Leonardi *et al*[25], 2017	M/66	NSCLC	N	Pembrolizumab	None	hyperglycemia Ketonuria	N	7.6% (4.2%–5.8%)	0.3 ng/mL	GAD+	12	Unavailable
Wong *et al*[26], 2020	F/55	Squamous cell lung carcinoma.	N	Atezolizumab	None	hyperglycemia Ketonuria	N	Unavailable	0.6nmol/L (0.19 ng/ml)	ZnT8+	8	Unavailable
Chokr *et al*[27], 2018	F/61	Melanoma	N	Nivolumab + ipilimumab,	None	DKA	N	6.90%	<0.1 ng/ml.	-	9	Unavailable
Chan *et al*[28], 2017	M/74	Melanoma	N	Nivolumab + ipilimumab	None	DKA	Transaminitis	Unavailable	Unavailable	-	14	Unavailable
Zezza *et al*[29], 2019	F/60	Melanoma	T2DM	Nivolumab + ipilimumab	None	DKA	N	7.60%	Unavailable	GAD+ICA+, IA2+	2	Unavailable
Zezza *et al*[29], 2019	F/80	Melanoma	N	Nivolumab + ipilimumab	None	DKA	Thyroiditis	Unavailable	Unavailable	GAD+	3	Unavailable
Shibayama *et al*[30], 2019	F/79	Merkel cell carcinoma	N	Avelumab	None	Hyperglycemia Ketonuria	N	7.50%	<0.1 ng/mL	-	20	High risk: DRB1 *09:01:02 DRB1 *14:54:01 DQA1 *01:04 DQA1 *03:02 DQB1 *05:02:01 and DQB1 *

												03:03:02
Marchand *et al*[21], 2019	M/65	Melanoma	N	Nivolumab	None	DKA	Hashimoto	8.5% (74 mmol/mol)	<0.1 ng/mL	-	34	High risk: DRB1*04:01 DQA1*02 DQB1*02:02 DRB1*07:01 DQA1*03 DQB1*03:01
Okamoto *et al*[31], 2016	F/55	Melanoma	N	Nivolumab	Acarbazine, + nimustine, + cisplatin + tamoxifen	Hyperglycemia Ketonuria	N	7.00%	1.0 ng/mL	-	48	High risk: DRB1*04:05-DQB1*04:01
Godwin *et al*[32], 2017	F/34	NSCLC	N	Nivolumab	Carboplatin + pemetrexed	DKA	N	7.1% (normal range 4.6–6.1%)	<0.1 ng/mL	GAD+, IA2+ ZnT8+	3	A30:01, 30:02 (A30) D09:CTZ, 09:CTZ (DR9)
Smith-Cohn *et al* [33], 2017	F/66	Cholangiocarcinoma	N	Pembrolizumab	None	Hyperglycemia	N	8.7% (4.2%–5.8%)	Unavailable	GAD+	12	Unavailable
Marchand *et al*[21], 2019	M/83	Melanoma	N	Pembrolizumab	None	Hyperglycemia	Hashimoto's disease	9.40%	1.0 ng/mL	-	12	DRB1*01:01 DQA1*01 DQB1*05:01/ DRB1*16:01 DQA1*01 DQB1*05:02
Maamari *et al*[34], 2019-3	F/47	Cardiac angiosarcoma	N	Pembrolizumab	Ifosfamide, gemcitabine, docetaxel	DKA	N	6.40%	0.1 ng/mL	GAD+	3	Unavailable
Tassone *et al*[35], 2019-9	M/42	Pulmonary adenocarcinoma	N	Nivolumab	None	DKA	N	Unavailable	0.2 ng/dL (2ng/ml)	GAD+	12	DRB1*03:15-DQB1*02:06
Yilmas *et al*[36], 2020-8	M/49	Renal cell carcinoma	N	Nivolumab	None	DKA	N	10.90%	2.4 ng/mL	-	44	Unavailable
Wen *et al*[37], 2020	M/56	Hepatocellular carcinoma	N	Sintilimab	None	DKA	N	7.80%	1.12 ng/mL	-	24	DRB1*12:01 DRB1*12:02; DQB1 *05:03 DQB1 *03:01; DQA1 *01:04 DQA1 *06:01

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GAD: Anti-glutamic acid decarboxylase antibody; HLA: Human leukocyte antigen; irAE: Immune-related adverse effect; SCLC: Small cell lung cancer; NSCLC: Non-small cell lung cancer; DKA: Diabetic ketoacidosis; Ad: Adenocarcinoma; IAD: Isolated adrenocorticotropic hormone deficiency; N: None.

activating and restoring the function of T cells, which contributes to an obvious antitumor effect. Accordingly, some normal tissues have been damaged in this process by the increase of cytokines. ICI-DM has rarely been reported as an irAEs of anti-PD1/PD-L1 therapy, and primarily in case reports.

In our review of case reports, the main tumor types were melanoma (13/36, 36.1%) and non-SCLC (8/36, 22.2%). The different treatment regimens included monotherapy with anti-PD-1 (19/ 36, 52.7%) anti-PD-L1 (8/36, 22.2%) or a combination of anti-

Table 4 Characteristics of patients with diabetes induced by immune checkpoint inhibitors

Reported cases	*n* (%)
Tumor types	
Melanoma	13/36 (36.1)
NSCLC	8/36 (22.2)
Renal cell carcinoma	2/36 (5.6)
Squamous cell carcinoma	3/36 (8.3)
Other cancers	10/36 (27.8)
ICBs	
Anti PD-1	19/ 36 (52.7)
Nivolumab	12
Pembrolizumab	6
Sintilimab	1
Anti PD-L1	8/ 36 (22.2)
Avelumab	2
Atezolizumab	5
Durvalumab	1
Anti PD-1+CTLA-4	9/ 36 (25.0)
Nivolumab + ipilimumab	8
Pembrolizumab + ipilimumab	1
Demographic data	
Sex (F/M)	16/20
Average age (yr)	58.8
Time of diagnosis after start of (w)	14.6
Presentation	
DKA	29/36 (80.6)
Hyperglycemia Ketonuria	8/36 (22.2)
HbA1c, % (avg)	7.8 26/36
Relevant history	
T2DM	3/36 (8.3)
Hypothyroidism	2/36 (5)
Family history of T1DM	2/36 (5)
None	29/36 (80.5)
Antibodies	
GAD+	18/36 (50)
IA-2+	4/36 (10)
ZnT8+	2/36 (5)
Negative	12/36 (33.3)

NSCLC: Non-small cell lung cancer; PD-L1: Programmed death-ligand 1; DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GAD: Anti-glutamic acid decarboxylase antibody.

CTLA-4 with anti-PD-1 (9/36, 25.0%). Diabetic ketoacidosis (DKA) was the first sign of diabetes in 29 of 36 (80.5%) case reports, which is similar to 85.7% in another study [38], and the average time from initiation of anti-PD-1/PD-L1 therapy to diagnosis of

ICI-DM was 14.6 wk (range 2–48 wk). Low C-peptide levels were present at diagnosis in 82% (23/28) of cases. In addition, 26 of 36 patients presented with a median glycated hemoglobin level of 7.6% (average: 7.8%; range: 6.4%–10.9%), which is the same as in other studies[39,40]. Most of the patients did not have relevant autoimmune history, which was only seen in 18.3% of our reviewed cases. These case reports have different definitions for ICI-DM. Since the syndrome has similarities with classic type 1 (T1)DM, most reports simply classified ICI-DM as T1DM, but ICI-DM has its own features. We found several significant features of ICI-DM: (1) Abrupt onset of hyperglycemia, and low to absent insulin C-peptide levels; (2) Rapid destruction of islets β cells, leading to endogenous insulin deficiency; and (3) High risk of DKA[39]. In addition to the above features, ICI-DM does not have a "honeymoon period" like juvenile T1DM, nor does it have GADA as in latent autoimmune DM in adults[41].

Similar to a previous study[39], our autoantibody analysis was positive in 50% of patients for GADA. Some studies have demonstrated that GADA-positive patients developed ICI-DM in the first 2 mo after initiation of therapy, and GADA-negative patients developed ICI-DM after 2 mo of treatment[42]. Patients with any positive diabetes autoantibodies at the time of presentation of ICI-DM have fewer cycles than those with negative autoantibodies. Our results showed that GADA-positive patients had ICI-DM onset at an average of 8 wk after immunotherapy compared with 22.8 wk in GADA-negative patients. It has been demonstrated that the interval from initiation of anti-PD-1/PD-L1 therapy and onset of ICI-DM is related to the presence/absence of GADA. Serological examination of GADA prior to anti-PD-1/PD-L1 therapy might be helpful for predicting the development of ICI-DM. In addition, several major histocompatibility complex and HLA molecules are associated with increased susceptibility to T1DM, especially HLA-DRB1, -DQB1 and –DQA1[43]. Different combinations of DRB1, DQB1 and DQA1 determine the extent of haplotypic risk. The most susceptible HLA haplotypes are DRB1*0405–DQA1*0301–DQB1*0302, followed by DRB1*0401–DQA1*0301–DQB*0302, DRB1*0301–DQA1*0501–DQB1*0201, and DRB1*0402–DQA1*0301–DQB1*0302. Subsequently, DQB1*0302 allele is the key susceptibility allele[44]. However, another study confirmed that DPB1*0301 and DPB1*0202 are also susceptible haplotypes for T1DM. Hence, the HLA typing of our patient (Table 2) showed a high risk of T1DM. Based on this evidence, there were seven patients with high-risk genes for T1DM among 13 patients tested. Accordingly, understanding the association between HLA and the development of ICI-DM by anti-PD-1/PD-L1 therapy is significant in predicting susceptible patients. When clinical features are discordant with the results of autoantibody testing, genetic risk score (GRS) could be an important addition to diagnosis of ICI-DM. This GRS summarizes risk-associated variation across the genome of T1DM[45]. One limitation of our case was the lack of information before sintilimab, such as autoimmune antibodies and genetic factors like HLA genotypes that may predispose to endocrine irAEs.

Multiple studies have indicated both the PD-1 and CTLA-4 pathways in the pathogenesis of T1DM and suggest a synergistic effect between these two negative regulatory receptors to enhance autoimmune disorders. Furthermore, the incidence of ICI-induced endocrine irAEs is significantly higher in patients treated with combination immunotherapy compared with single immunotherapy. The incidence of thyroid dysfunction is high in patients treated with single PD-1 antibodies. In contrast, the incidence of hypophysitis is highest in patients treated with ipilimumab[46]. Similarly, our review also found that combination of PD-1 inhibitor and anti-CTLA-4 therapy causes endocrine dysfunction. The most common combination was nivolumab and ipilimumab. An animal study found that single CTLA-4 blockers in nonobese diabetic (NOD) mice only induced diabetes in baby mice, while PD-1 blocked secondary diabetes in NOD mice at any age[47]. A recent case reported that ipilimumab induced T1DM. The mechanism by which single anti-CTLA-4 therapy induced ICI-DM was unclear and needs further study[48]. However, a randomized, double-blind, phase 3 study suggested that combination of immunotherapy significantly increases progression-free survival more than monotherapy does[49]. Therefore, it is important for clinicians to consider whether to continue to use combination therapy when endocrine irAEs appear.

T1DM is caused by destruction of pancreatic β cells by virus infection, genetic factors and autoimmune disorders[32]. Accordingly, the main mechanism of ICI-DM may be islet cell damage. There is an active interaction between β cells and immune cells during insulitis. This kind of interaction usually has a largely negative effect on β cells. An animal study has shown that PD-1 deficiency accelerates the occurrence and frequency of T1DM in NOD mice, and infiltration of pancreatic islets by T cells with strong T helper 1 polarization[50]. In addition, animal and human experiments have shown that PD-L1 in insulin-positive cells of T1DM, but absent in nondiabetic

individuals and type 2 DM, is mainly due to islet β cell expression[6]. The present data indicate that interferon (IFN)-α and IFN-γ are the main regulators of PD-L1 expression in human pancreatic β cells, especially IFN-γ. IFN-γ suppresses autoreactive T cells by upregulating PD-L1. In other words, PD-L1 protects islet β cells to delay progression of DM and even prevent its onset[50-52]. Yet, IFN-α and IFN-γ induce proinflammatory responses. For instance, HLA class I upregulation, cytokine production and endoplasmic reticulum stress are harmful to the human body, including the pancreas. Inhibition of signal transducer and activator of transcription 2 can prevent IFNα-induced HLA class I expression, and at the same time allow PD-L1 upregulation[53], but this lacks clinical validation. Therefore, the level of PD-L1 expression may serve as an additional criterion for irAEs after ICI treatment. PD-L1 expression can also be used as a prognostic marker of immunotherapy[54]. In our patient, in spite of tumor necrosis factor-α, IL-1β and IFN-γ, all of the cytokines were normal during treatment with sintilimab, which suggest the particular pathogenic mechanism of ICI-DM. However, the precise mechanism mediating ICI-DM is still unclear. Further studies are required to elucidate the pathogenesis and background factors for this form of DM.

CONCLUSION

This is the second case of sintilimab-induced autoimmune DM. The first one was a recently published case report of autoimmune DM diagnosed in a patient with hepatocellular carcinoma[37]. What makes our case different from others is that there was no DKA in the process of DM. This may be because patients were regularly monitored for plasma glucose level. This illustrates the importance of regular monitoring of glucose during immunotherapy for inhibiting progression of DM. Furthermore, based on the information collected in our review, we recommend measuring PD-L1 expression, HLA typing, islet cell antibody testing, C peptide measurement, or even determining T1DM-associated GRS for clinicians before or during immunotherapy. We can compare symptom severity and therapeutic efficacy in DM patients with or without a history of DM after treatment with PD-1/PD-L1 inhibitors in the future, so as to evaluate whether patients with potential risk of DM are suitable for treatment with PD-1/PD-L1 inhibitors.

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