Programmed Cell Death-1 Inhibitor–Induced Type 1 Diabetes Mellitus

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Context: Pembrolizumab (Keytruda; Merck Sharp & Dohme) is a humanized IgG4 monoclonal antibody used in cancer immunotherapy. It targets the programmed cell death-1 (PD-1) receptor, which is important in maintaining self-tolerance. However, immune checkpoint blockade is associated with a risk for immune-related adverse events (irAEs) potentially affecting the endocrine organs. Type 1 diabetes mellitus is a rare irAE of PD-1 inhibitors, occurring in 0.2% of cases.

Evidence Acquisition: Systematic search of four databases (MEDLINE, Embase, Web of Science, and Cochrane Library) using the search terms "diabetes" or "ketoacidosis" and "pembrolizumab," "nivolumab," "PD-1 inhibitor," or "immunotherapy." Included were articles published in English between 1 January 2012 and 1 January 2018. The search was supplemented by bibliographic searches of the complete reference lists of all included papers.

Evidence Synthesis: We provide an overview of all published cases (n = 42) of PD-1 inhibitor–induced type 1 diabetes mellitus to date, including a well-characterized case of islet cell antibody and glutamic acid decarboxylase antibody–positive diabetes mellitus, in a patient with a diabetes-prone HLA genotype. She presented with diabetic ketoacidosis during pembrolizumab therapy for a metastatic uveal melanoma. Furthermore, we discuss potential pathogenic mechanisms, clinical presentation, prognostic markers (β-cell antibodies and HLA type), treatment, and a screening protocol.

Conclusions: Because the use of immunotherapy will increase, it is essential that all clinicians are aware of diabetic ketoacidosis as a rare and life-threatening side effect of immunotherapy. Blood glucose monitoring during anti–PD-1 therapy is necessary. (***J Clin Endocrinol Metab*** **103: 3144–3154, 2018)**

Cancer immunotherapy is a successful and fast-growing field. Pembrolizumab (Keytruda; Merck Sharp & Dohme) and nivolumab (Opdivo; Bristol-Myers Squibb) are two IgG4 monoclonal antibodies (mAbs) targeting the programmed cell death-1 (PD-1) receptor (1–4). This receptor is important in maintaining self-tolerance and therapeutically targeted by immune checkpoint–inhibiting mAbs to enhance antitumor immune responses. They have been approved for malignant melanoma and several other cancer types, including non–small cell lung cancer, squamous cell carcinoma of the head and neck, classical Hodgkin lymphoma, advanced urothelial carcinoma, advanced gastric cancer, and microsatellite instability-high or mismatch-repair–deficient solid tumors.

Because of the widespread use of immunotherapy across cancer types and even more cancer types being

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Abbreviations: DKA, diabetic ketoacidosis; GADA, glutamic acid decarboxylase antibody; IA2A, insulinoma antigen-2 antibody; ICA, islet cell antibody; irAE, immune-related adverse event; mAb, monoclonal antibody; NOD, nonobese diabetic; PD-1, programmed cell death-1.

studied, the use of immunotherapy is still expected to increase in the following years. However, immunotherapy is known for its immune-related adverse events (irAEs). Known side effects are pneumonitis, colitis, hepatitis, dermatitis, nephritis, pancreatitis, vitiligo, rash, pruritus, and endocrinopathies, including thyroiditis [pembrolizumab: 0.6% (2); nivolumab: 8.6% (5)], hypothyroidism [pembrolizumab: 7.9%; nivolumab: 6.5% (6)], hyperthyroidism [pembrolizumab: 3.8%; nivolumab: 2.5% (6)], hypophysitis [pembrolizumab: 0.6% (2), nivolumab: 0.6% (7)], and diabetes mellitus (1). Even though only few patients develop irAEs, these can be life threatening and demand immediate recognition and therapy. Autoimmune diabetes mellitus and the associated diabetic ketoacidosis (DKA) are examples of rare irAEs [pembrolizumab: 0.2% (2); nivolumab monotherapy: 0.9% (7)].

In this review, we provide an overview of all published cases (n = 42) of PD-1 inhibitor–induced type 1 diabetes mellitus, including a new case subject who presented with DKA during pembrolizumab therapy for a metastatic uveal melanoma. Furthermore, we discuss potential pathogenic mechanisms, clinical presentation, prognostic markers (β-cell antibodies and HLA type), treatment, and a screening protocol.

Association Between PD-1 and Diabetes

Immunotherapy

Type 1 diabetes mellitus is a rare irAE of PD-1 inhibitors. PD-1 is a receptor expressed on T cells that can be activated by two ligands: PD-L1 (B7-H1 or CD274) and PD-L2 (B7-DC or CD273). PD-1 is not only expressed on T cells but also on other hematopoietic cells (B cells, dendritic cells, macrophages, *etc.*) as well as vascular endothelial cells and, most importantly, pancreatic islet cells (8). When PD-1 binds to PD-L1, an inhibitory signal is generated that regulates T-cell activation, tolerance, and cytotoxic activity. This binding suppresses the immune system and can induce apoptosis of T cells.

Tumors try to evade the human immune system by developing an immunosuppressive tumor microenvironment and the activation of inhibitory pathways that suppress a tumor-specific T-cell response. One of these inhibitory pathways is the PD-1–PD-L1 pathway (9). Certain tumors express PD-L1 and hereby evade immune response. Based on this mechanism, anti–PD-1 and anti–PD-L1 checkpoint inhibitors have been developed. These molecules block the PD-1 pathway and thereby restore T-cell function and antitumor immune response (3, 4). However, when the PD-1 pathway is blocked, not only T cells targeting cancer, but also autoreactive T cells such as those targeting pancreatic islet cells survive, causing type 1 diabetes.

PD-1 expression on activated and exhausted T cells

T-cell exhaustion is a state that can appear during long-term antigen exposure such as in chronic infections or cancer. When CD8-positive T cells fail to eliminate infections or tumors, chronic antigen stimulation leads to their exhaustion. This state is characterized by T-cell dysfunction, loss of proliferative capacity, and impaired cytokine production and effector function (8, 10). Complex mechanisms are involved in this T-cell dysfunction, but PD-1 plays an important role in T-cell exhaustion. It has been shown that exhausted T cells upregulate inhibitory receptors, including PD-1, CTLA-4, Tim-3, LAG-3, *etc.* (8, 10). However, T cells that upregulate inhibitory receptors are not always exhausted or dysfunctional. Inhibitory receptors are also transiently upregulated upon T-cell activation (8). Blockade of the PD-1 pathway (by anti–PD-1 mAbs like nivolumab and pembrolizumab) can reinvigorate these exhausted T cells, resulting in better control of cancer (4, 10).

Responders and nonresponders to PD-1 therapy

Several biomarkers for response to anti–PD-L1 therapy have been studied, including PD-L1 expression and the presence of tumor-infiltrating lymphocytes.

First, high PD-L1 expression in tumors has been associated with higher response rates, especially when PD-L1 was expressed by tumor-infiltrating immune cells (11). However, not all studies found this positive correlation. Several factors can explain these discrepant findings among studies, including heterogeneity of intratumor and intertumor (primary vs metastatic) PD-L1 expression; location of signal (membrane, intracellular, and stromal); changes in expression between biopsy and treatment; differences in detection methods, including discordance between antibodies and staining conditions; and different cutoffs used to assess positivity (9, 11).

Second, markers of preexisting immunity such as tumor inflammation and presence of tumor-infiltrating lymphocytes have also been associated with higher response rates (9, 10).

Association Between PD-1 and Diabetes

Type 1 diabetes mellitus is caused by destruction of insulin producing β-cells by autoreactive T cells. Several mouse model studies have studied the role of PD-1 in the development of type 1 diabetes. PD-1 and PD-L1 blockade precipitate diabetes in prediabetic nonobese diabetic (NOD) mice (12–14). Anti–PD-1 drugs might have the same effect, and the reduction of PD-1 might activate autoreactive T cells, resulting in an autoimmune response against pancreatic islet cells (15, 16).

Furthermore, recent evidence in humans demonstrated that patients with type 1 diabetes mellitus have a substantial reduction in PD-1 expression in $CD4^+$ T cells compared with healthy control subjects. This may indicate that lower PD-1 expression in $CD4^+$ T cells might contribute to the development of type 1 diabetes through T-cell activation (17).

Based on the reviewed literature, we hypothesize that the onset of diabetes is due to an autoreactive $CD8^+$ T-cell clone that is activated when pembrolizumab therapy is started and the PD-1 pathway becomes blocked. The PD-L1 molecules of the pancreatic β-cells are then unable to bind the PD-1 receptor on autoreactive T cells, because they are blocked by pembrolizumab. Because of this disinhibition of the autoreactive T cells, the autoreactive T cells can survive and destroy the β-cells (18). Figure 1 provides an overview of the mechanism of action of PD-1 immune checkpoint inhibitors and the hypothesis of association between PD-1 immune checkpoint inhibitors and type 1 diabetes mellitus.

Case Report

We present a 73-year-old woman with a history of a uveal melanoma of the right eye. She underwent an enucleation of the eye in September 2015. Follow-up after surgery showed good clinical result with no signs of metastatic disease on further imaging (^{18}F-fluorodeoxyglucose positron emission tomography-CT).

In March 2017, she presented with right-sided abdominal pain due to new metastatic liver disease. Subsequently, treatment with Keytruda (pembrolizumab) was started. The patient was treated in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice, and General Data Protection Regulation and in accordance with all applicable regulatory and ethics committee requirements. She received two infusions of pembrolizumab (2 mg/kg

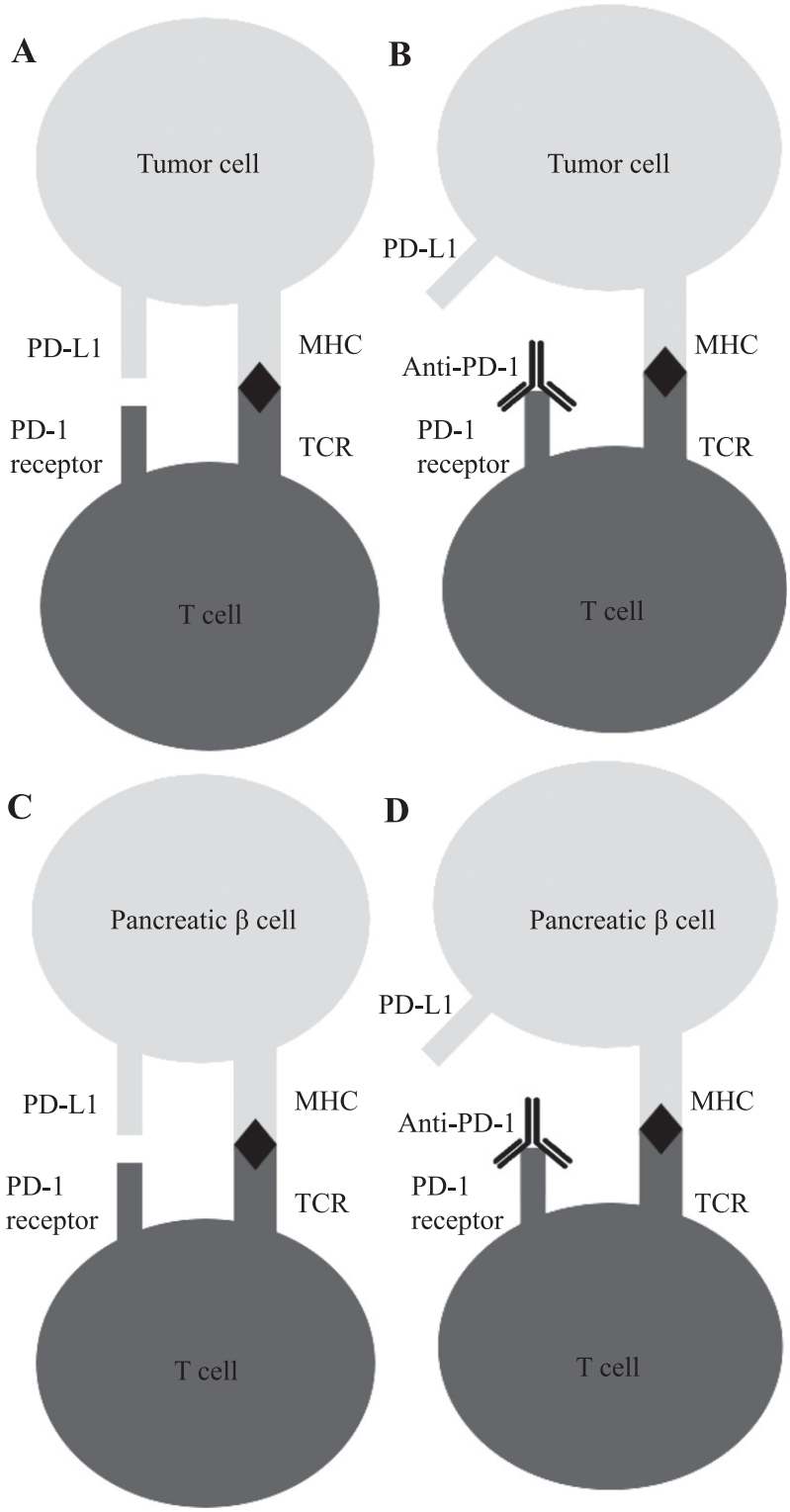

Figure 1. Mechanism of action of PD-1 immune checkpoint inhibitors and hypothesis of association between PD-1 immune checkpoint inhibitors and diabetes mellitus type 1. (A) Tumor cells can inactivate T cells and evade the immune system by expressing PD-L1. This leads to the enhanced survival of tumor cells. (B) Anti–PD-1 can block the PD-1 receptor and restore immune response. This leads to the apoptosis of tumor cells. (C) Pancreatic β-cells express PD-L1 and thereby evade the immune response. (D) During anti–PD-1 therapy, in certain susceptible persons, T cells are activated and develop an immune response to pancreatic β-cells. MHC, major histocompatibility complex; TCR, T-cell receptor.

every 3 weeks). Two weeks after the second infusion, she presented with complaints of anorexia, vomiting, polydipsia, and headache at the emergency department. DKA was diagnosed; she had a glycemia of 540 mg/dL, and arterial blood gas values showed a pH of 7.10 and very low bicarbonate of 6.8 mmol/L. Capillary β-hydroxybutyrate levels were 6.9 mmol/l. Lipase level was 81 U/L (normal: 73 to 393 U/L). Autoimmune adrenalitis was ruled out by a normal 250-μg cosyntropin test result (cortisol rising up to 292 ng/mL; normal response >180 ng/mL). Due to the initial presentation with vomiting and headache, hypopituitarism (due to hypophysitis, which may occur in up to 1.5% of patients) also needed to be ruled out. The patient had a normal pituitary function (TSH, 0.94 mU/L; free T4, 16.2 pmol/L; prolactin, 76.4 μg/L; and FSH, 47.3 U/L). MRI of the pituitary gland also revealed no abnormalities (no enhancement on T2-weighted images and no thickened pituitary stalk).

After a 24-hour stay in the intensive care unit being treated according to our hospital DKA protocol, the patient was transferred to the department of endocrinology under a low dose of continuous IV insulin. Further testing revealed an HbA_{1c} level of 7.1% (54 mmol/mol) and C-peptide of 0.11 nmol/L (0.3 ng/mL). This suggests sudden deterioration in glycemic control, corresponding to the pathophysiologic mechanism of type 1 diabetes mellitus. Investigation of β-cell autoantibodies showed positive islet cell antibodies (ICAs) of 400 JDF units (normal <12) and an elevated glutamic acid decarboxylase antibody (GADA) of 27,881 World Health Organization U/mL (normal <23). Insulinoma antigen-2 antibodies (IA2As), zinc transporter 8 antibodies (ZnT8A), and insulin antibodies were negative. HLA typing revealed DQA3-DQB3.2/DQA3-DQB3.2, which is a susceptible genotype.

A basal bolus multiple daily injection schedule was started with good glycemic control. After glycemic recuperation, a third session of pembrolizumab was given (without delay), resulting in no new side effects. Follow-up during further pembrolizumab therapy showed stable disease after five infusions.

Overview of Reported Cases

So far, to the best of our knowledge, 42 cases of immunotherapy-induced type 1 diabetes mellitus have been reported, including the current case report. Tables 1 and 2 summarize key findings.

Presentation

Patients presented with variable symptoms, ranging from asymptomatic hyperglycemia, polyuria, and polydipsia to severe DKA. DKA was the first sign of diabetes in 30 out of 35 (85.7%) case subjects reported with sufficient information about presentation. Two patients presented with ketonuria, but no ketoacidosis.

Time from initiation of anti–PD-1 therapy to diagnosis of diabetes mellitus ranged from 1 week to 52 weeks, and this corresponded to 1 to 17 infusions of immune checkpoint inhibitors. The median time to development of type 1 diabetes mellitus was three infusions or 6 weeks. Our patient developed DKA 2 weeks after the second infusion.

Autoantibodies

Based on the 42 reported cases, there is no clear pattern of diabetes-related autoantibodies. Approximately half of the tested case subjects (22 out of 39 or 56%) had detectable diabetes-related autoantibodies. In those 22 cases, GADAs were positive in all subjects, tyrosine phosphatase autoantibodies (IA2A) in 4 out of 20, ICA in only 2 patients, and insulin autoantibodies and ZnT8 antibodies in only 1 subject. Three other cases have been reported, however, without antibody status.

This observation corresponds to the results of the NOD mouse model of autoimmune diabetes of Ansari *et al.* (12). They observed no correlation between insulin autoantibody levels and development of autoimmune diabetes in NOD mice treated with PD-1–PD-L1 blockade. Certain mice developed diabetes without antibodies, whereas others developed antibodies but did not develop diabetes (12).

Furthermore, it should be taken into account that, whereas the presence of GADA and IA2A can aid in the diagnosis of type 1 diabetes, they are only present in up to 85% of patients with adult-onset type 1 diabetes (19). Moreover, GADA can also be positive in other autoimmune endocrine disorders such as autoimmune thyroid disease (20) and are therefore less specific than ICAs. Our patient was positive for both GADA and ICA.

Usui *et al.* (21) suggest that the interval from the start of treatment with anti–PD-1/PD-L1 antibodies to the onset of type 1 diabetes mellitus is related to the presence or absence of GADA. Their hypothesis was that GADA-positive patients developed type 1 diabetes mellitus earlier, in the first 2 months after the start of therapy, whereas GADA-negative patients developed type 1 diabetes mellitus later, after 2 months of therapy (21). In line with the observation of Usui *et al.* (21), Gauci *et al.* (22) found that the median interval from immunotherapy initiation to diagnosis of diabetes was 3 weeks in GADA-positive case subjects vs 12.5 weeks in GADA-negative case subjects (data from the 24 patients). Our case also supports the hypothesis that the interval between the start of anti–PD-1/PD-L1 antibodies to the onset of autoimmune diabetes might be related to the presence

Table 1. Reported Cases

Authors, Y (Reference)	Sex	Age (y)	Malignancy	DKA	HbA_{1c}	Therapy
Brahmer *et al.*, 2012 (44)	NR	NR	NR	NR	NR	c
Gaudy *et al.*, 2015 (27)	F	44	CM	+	6.8% (52 mmol/mol)	p
Mellati *et al.*, 2015 (28)	M	70	NSCLC	+	9.8% (84 mmol/mol)	c
Mellati *et al.*, 2015 (28)	F	66	SSCC	+	9.4% (79 mmol/mol)	c
Martin-Liberal *et al.*, 2015 (36) and Spain *et al.*, 2016 (37)	F	54	CM	+	NR	p
Hughes *et al.*, 2015 (29)	F	64	CM	K	7.4% (57 mmol/mol)	p
Hughes *et al.*, 2015 (29)	F	55	CM	+	6.9% (52 mmol/mol)	n
Hughes *et al.*, 2015 (29)	F	83	NSCLC	+	7.7% (61 mmol/mol)	n
Hughes *et al.*, 2015 (29)	M	63	RCC	−	8.2% (66 mmol/mol)	n
Hughes *et al.*, 2015 (29)	M	58	SCLC	+	9.7% (83 mmol/mol)	n
Hansen *et al.*, 2016 (30)	M	58	CM	NR	9.7% (83 mmol/mol)	p
Teramoto *et al.*, 2017 (46)	F	63	CM	+	8.9% (74 mmol/mol)	n
Humayun and Poole, 2016 (34)	M	55	CM	+	10.7% (93 mmol/mol)	p
Miyoshi *et al.*, 2016 (45)	F	66	CM	+	<8.7% (< 72 mmol/mol)	n
Okamoto *et al.*, 2016 (15)	F	55	CM	K	7.0% (53 mmol/mol)	n
Aleksova *et al.*, 2016 (38)	M	60	CM	+	7.1% (54 mmol/mol)	p
Chae *et al.*, 2017 (42)	M	76	NSCLC	−	5.8% (40 mmol/mol)	p
Lowe *et al.*, 2016 (23)	M	54	CM	+	NR	n + i
Hofmann *et al.*, 2016 (31)	F	58	CM	NR	NR	p
Hofmann *et al.*, 2016 (31)	F	70	CM	NR	NR	n
Hofmann *et al.*, 2016 (31)	F	78	CM	+	NR	n
Hofmann *et al.*, 2016 (31)	M	40	NR	NR	NR	n
Alhusseini and Samantray, 2017 (32)	M	56	NSCLC	+	8.5% (69 mmol/mol)	p + i
Hao *et al.*, 2017 (18)	F	28	CM	+	NR	n
Shah *et al.*, 2016 (41)	F	77	NSCLC	+	10.2% (88 mmol/mol)	n
Farrell *et al.*, 2017 (47)	M	30	CM	+	7.4% (57 mmol/mol)	p
Thoreau *et al.*, 2017 (48)	M	73	CM	+	8.5% (69 mmol/mol)	p
Godwin *et al.*, 2017 (24)	F	34	NSCLC	+	7.1% (54 mmol/mol)	n
Usui *et al.*, 2017 (21)	M	31	NSCLC	+	6.4% (46 mmol/mol)	n
Usui *et al.*, 2017 (21)	F	62	NSCLC	NR	6.5% (48 mmol/mol)	n
Munakata *et al.*, 2017 (49)	M	72	HL	−	7.3% (56 mmol/mol)	n
Alzenaidi *et al.*, 2017 (50)	M	46	CM	+	8.0% (64 mmol/mol)	n + i
Ishikawa *et al.*, 2017 (51)	F	54	CM	NR	7.0% (53 mmol/mol)	n
Leonardi *et al.*, 2017 (43)	M	66	NSCLC	+	7.6% (60 mmol/mol)	p
Li *et al.*, 2017 (33)	M	63	NSCLC	+	7.2% (55 mmol/mol)	n
Gauci *et al.*, 2017 (22)	M	73	CM	+	8.8% (73 mmol/mol)	n
Scott *et al.*, 2018 (52)	M	58	NR	+	6.8% (50 mmol/mol)	p + i
Kapke *et al.*, 2017 (53)	M	83	SCC	+	7.4% (57 mmol/mol)	n
Kapke *et al.*, 2017 (53)	F	63	UC	+	7.8% (61 mmol/mol)	a
Araujo *et al.*, 2017 (54)	F	73	NSCLC	+	7.2% (55 mmol/mol)	n
Zaied *et al.*, 2018 (55)	M	±70	RCC	+	8.4% (68 mmol/mol)	n
Current patient	F	73	UM	+	7.1% (54 mmol/mol)	p

(*Continued*)

of GADA. Based on the clinical data of the reviewed literature, the median interval from immunotherapy initiation to diagnosis of diabetes was 5 weeks in GADA-positive case subjects vs 9 weeks in GADA-negative case subjects (data from 42 patients).

In certain cases, a seroconversion was witnessed (23), but in other cases, autoantibodies were already present before the start of immunotherapy (22, 24). In our case, we cannot comment on seroconversion because serum samples before start of immunotherapy were not

Table 1. Reported Cases (Continued)

Type 1 Diabetes Onset Time (Number of Infusions)	Type 1 Diabetes Onset Time (wk)	Antibodies	C-Peptide	Reference Range C-Peptide	HLA Typing
NR	NR	NR	NR	NR	NR
2	/	−	Undetectable	NR	NHR
5	15	−	0.3 ng/mL	1.0–7.1 ng/mL	NR
3	7	GAD+	<0.1 ng/mL	1.0–7.1 ng/mL	High risk: DR3-DQ2(HLA-DQB1*02)/ DR4-DQ8
3	NR	GAD+	NR	NR	High risk: DRB1*04 and DQB1*03:02 (HLA-A2 DR4 DQ8)
NR	4	−	0.5 ng/mL	1.1–4.4 ng/mL	High risk: DR4+
NR	20	NR	<0.1 ng/dL	1.1–4.4 ng/mL	High risk: A2.I+, DR4+
NR	4	GAD+	<0.1 ng/dL	1.1–4.4 ng/mL	High risk: A2.I+, DR4+
NR	16	GAD+, ICA+, IAA+	1.3 ng/dL	1.1–4.4 ng/mL	High risk: A2.I+, DR4+
NR	1	GAD+	<0.1 ng/dL	1.1–4.4 ng/mL	High risk: A2.I+
17	52	GAD+	2.4 ng/mL	NR	NR
8	NR	−	0.08 ng/mL	NR	NR
9	NR	−	NR	NR	NR
6	17	−	0.23 ng/mL	0.8–2.3 ng/mL	NHR
NR	52	−	<0.1 ng/mL	0.61–2.09 ng/mL	High risk: DRB1*04:05-DQB1*04:01
2	5	−	57 pmol/L	300–2350 pmol/L	NR
2	NR	GAD+, IA2A+	0.81 ng/mL	0.9–3.85 ng/mL	NR
3	NR	GAD+	<0.1 ng/mL	NR	NHR
1	3	GAD+	Low	NR	NR
4	6	−	<16 pmol/L	140–830 pmol/L	NR
2	3	GAD+	Low	NR	NR
NR	6	NR	NR	NR	NR
1	3	GAD+, IA2A+	Undetectable	NR	NR
3	NR	GAD+	NR	NR	High risk: DR3 DQ3
1	2	−	0.81 ng/mL	NR	NHR
NR	NR	−	Undetectable	NR	NR
NR	26	−	NR	NR	NR
2	NR	GAD+	<0.1 ng/mL	0.8–3.85 ng/mL	NHR
1	2	GAD+	<0.03 ng/mL	>0.03 ng/mL	High risk: DRB1*04:05-DQB1*04:01
4	NR	−	NR	NR	High risk: DRB1*09:01-DQB1*03:03
5	NR	−	NR	NR	NR
2	NR	GAD+	0.2 ng/mL	0.9–5.5 ng/mL	NR
16	NR	−	<0.1 ng/mL	0.8–2.5 ng/mL	Risk unknown: HLA-B*15:01, *40:06, DRB1*04:05, *04:06, DQB1*03:02, and *04:01
3	NR	GAD+	0.3 ng/mL	1.1–4.4 ng/mL	NR
NR	4	GAD+	NR	NR	NR
3	6	GAD+, ZnT8A+	0 nmol/L	0.5 ng/mL	NR
3	9	−	NR	NR	NR
6	12	GAD+	0.32 ng/mL	1.1–4.4 ng/mL	NHR: DRB1*08, DRB1*11, DQB1*03, DQB1*04, DQA1*04, DQA1*05
9	24	GAD+	0.02 ng/mL	1.1–4.4 ng/mL	High risk: DRB1*03, DRB1*04, DQB1*02, DQB1*03, DQA1*03, DQA1*05
2	4	GAD+	0.06 ng/mL	<0.1 ng/mL	High risk: DRB1*03:01-DQA1*05:01-DQB1*02:01/DRB1*04:01-DQA1*03:01-DQB1*03:02
3	6	−	0.4 ng/mL	1.1–4.4 ng/mL	NR
2	8	GAD+, ICA+	0.11 nmol/L (0.3 ng/mL)	0.26–1.03 nmol/L (0.8–3.1 ng/mL)	High risk: DQA1*0301-DQB1*0302/ DQA1*0301-DQB1*0302

HLA information is not consistently presented in terms of nomenclature, or alleles reported, because of limitation of what was reported in literature.

Abbreviations: −, negative; +, positive; a, atezolizumab; c, unspecified anti–PD-L1 antibody; CM, cutaneous melanoma; F, female; HL, Hodgkin lymphoma; i, ipilimumab; IAA, insulin autoantibody; K, ketonuria; M, male; n, nivolumab; NHR, no high-risk type; NR, not reported; NSCLC, non–small cell lung cancer; p, pembrolizumab; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SSCC, sarcomatoid squamous cell carcinoma; UC, urothelial carcinoma of the bladder; UM, uveal melanoma.

Table 2. Characteristics of Reported Patients With Immunotherapy-Associated Type 1 Diabetes

Reported cases	42
Causative agent	
Nivolumab	21
Pembrolizumab	12
Nivolumab plus ipilimumab	2
Anti–PD-L1	2
Anti–PD-1	1
Pembrolizumab plus ipilimumab	2
Atezolizumab	1
Demographic data	
Sex (men/women/not reported)	21/20/1
Age, y	63 (28–83)
Presentation	
DKA	30 (71.4)
Hyperglycemia (negative for DKA)	3
HbA_{1c}, %	7.5 (6.4–10.7)
HbA_{1c}, mmol/mol	58.5 (46–93)
Time of diagnosis after start of immunotherapy	
Number of doses	3 (1–17)
Onset in wk	6 (1–52)
β-Cell antibodies, n positive/n tested (%)	
GAD	22/39 (56)
IA2A	4/20 (20)
ICA	2/16 (12.5)
IAA	1/16 (6.2)
ZnT8A	1/6 (17)
Undetectable or low serum C-peptide	30/32 (93)
High-risk HLA haplotypes	14/21 (67)
Personal history of autoimmune disease	12/42 (28.6)

Data are median (range) or number (%) unless otherwise noted.

Abbreviation: IAA, insulin autoantibody.

available. In the case report published by Lowe *et al.* (23), the patient exhibited an undetectable GADA titer 1 month prior to start of treatment with combination ipilimumab/nivolumab. This raised to 0.38 nmol/L (normal <0.02 nmol/L) at diagnosis of autoimmune diabetes. In contrast, in the case report of Gauci *et al.* (22), retrospective investigations on serum for 3 months before the start of nivolumab already showed the presence of autoantibodies but normal insulin, C-peptide secretion, and glycaemia (22). Similarly, in the patient reported by Godwin *et al.* (24), diabetes-related autoantibodies were already present prior to anti–PD-1 therapy.

HbA_{1c} and C-peptide

Serum C-peptide was low or undetectable at diagnosis or during follow-up in 30 out of 32 tested patients. HbA_{1c} levels vary within the reported cases from 6.4% to 10.7% (46 to 93 mmol/mol). The low or undetectable C-peptide combined with the moderately low HbA_{1c} levels probably indicate the fulminant onset of diabetes with rapid β-cell destruction and a shorter duration of hyperglycemia. Similarly, in our patient, there was a low C-peptide level, and HbA_{1c} was moderately increased (7.1% or 54 mmol/mol).

Other autoimmune diseases

Twelve out of 42 patients reported an autoimmune-mediated disease or reaction before, during, or after the immune checkpoint inhibitor therapy. This might suggest that patients sensitive or predisposed to the development of autoimmune disease are more prone to develop irAEs after initiation of immune checkpoint inhibitors, including autoimmune diabetes mellitus. In addition, individuals with one autoimmune disease are at higher risk of a second autoimmune disorder (25, 26). We suggest increasing vigilance for such patients. However, the decision whether to start immune checkpoint inhibitor therapy in patients with a preexisting autoimmune disease will probably not be affected because the considerable beneficial effects outweigh the disadvantages of irAEs.

Ten case reports mentioned thyroid disease (22, 23, 27–33). In our patient, thyroid function was normal. Because our patient presented with vomiting and headache, other known irAEs of anti–PD-1 therapy, such as hypophysitis and autoimmune adrenalitis (Addison disease), needed to be investigated and were ruled out. In the literature, two cases have been reported of patients who developed hypophysitis and autoimmune diabetes mellitus during immune checkpoint inhibitor therapy (23, 34). Addison disease is known to occur in 0% to 8% of patients treated with anti–PD-1 or anti–PD-L1 therapy (1). However, this side effect was also not present in the 42 reported case subjects. Recently, the first case of central diabetes insipidus was reported (35).

Age of onset

In the 42 case subjects, the median age at diagnosis was 63 years (range 28 to 83). This late age onset is atypical for type 1 diabetes mellitus, which is usually diagnosed at an age <40 years. It is even late for late autoimmune diabetes of the adult. Based on the age of onset, these patients with immune checkpoint inhibitor–induced diabetes mellitus might be easily misclassified as having type 2 diabetes. However, the high incidence of ketoacidosis suggests type 1 diabetes.

HLA types

Certain HLA types predispose to type 1 diabetes, including the high-risk genotype DQA3-DQB3.2/DQA4-DQB2 (DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201) in Caucasians. HLA typing of our patient revealed DQA1*0301-DQB1*0302/DQA1*0301-DQB1*0302, which is a susceptible genotype.

Fourteen out of 21 tested patients had an HLA genotype with increased risk for diabetes (15, 18, 21, 28, 29, 36, 37). Therefore, based on pathogenetic and clinical data of the reviewed literature, it is conceivable to suggest that patients with high-risk HLA, and thus a genetic predisposition for type 1 diabetes mellitus, have an increased risk for the development of immune checkpoint inhibitor–induced diabetes mellitus.

Antitumor response

Although this group of case reports is probably too small to draw definitive conclusions, it is noticeable that most patients who developed type 1 diabetes secondary to a PD-1 inhibitor also reached an antitumor response (38).

Even though further validation is required, Judd *et al.* (39) demonstrated that for a subset of patients with nonmelanoma treated with PD-1 checkpoint inhibitors, in particular those with low-grade irAEs, irAEs were predictive for an improved response rate and longer time to next therapy and longer survival (39). This confirmed the study by Freeman-Keller *et al.* (40), who observed that cutaneous irAEs (rash and vitiligo) were associated with improved survival in patients with melanoma treated with nivolumab. However, they observed no noteworthy survival differences with other irAEs (endocrinopathies, colitis, or pneumonitis) (40). Considering these observations, it would be of interest to study this in larger prospective trials, because this information is clinically very relevant.

Therapy of PD-1–induced autoimmune diabetes

In contrast to other irAEs, which are mostly treated with high-dose corticosteroids or TNF-α inhibitors, there is no treatment of autoimmune diabetes mellitus. One research group reported their attempt of treatment with oral prednisolone at 2 mg/kg for 3 days and then 1 mg/kg for 10 days with a weaning schedule for a total of 6 weeks treatment, the standard irAE therapy. Despite their attempt, glucose control deteriorated, and they did not observe benefit from this therapy. However, they believe that other immunosuppressive agents, such as mAbs, which are not toxic to the pancreatic islet cells, might be more effective, and therefore, future research is needed to determine their efficacy (38). However, type 1 diabetes manifests itself when up to 80% to 95% of pancreatic β-cells have been destroyed. With such a considerable loss of β cells, it seems unlikely that immunotherapy dose modification or immunosuppression with corticosteroids would alter the course of disease. Currently, the treatment of immunotherapy-induced diabetes and DKA remains standard insulin therapy.

After the start of insulin therapy, glycemic control was reached in almost all cases. However, three cases reported challenging control with severe instability of blood glucose and frequent and unpredictable hypoglycemic and/or ketoacidosis episodes (24, 33, 41).

In most cases, immunotherapy was immediately restarted after glycemia was controlled. Restarting the immunotherapy did not cause a change in glycemia, and the patients kept stable insulin requirements and fasting blood glucose levels. Also in our patient, resuming the checkpoint inhibitor did not worsen glycemic control.

Proposal of a screening strategy

Because the use of immune checkpoint inhibitors will continue to rise, clinicians (general practitioners, emergency physicians, oncologists, and endocrinologists) must

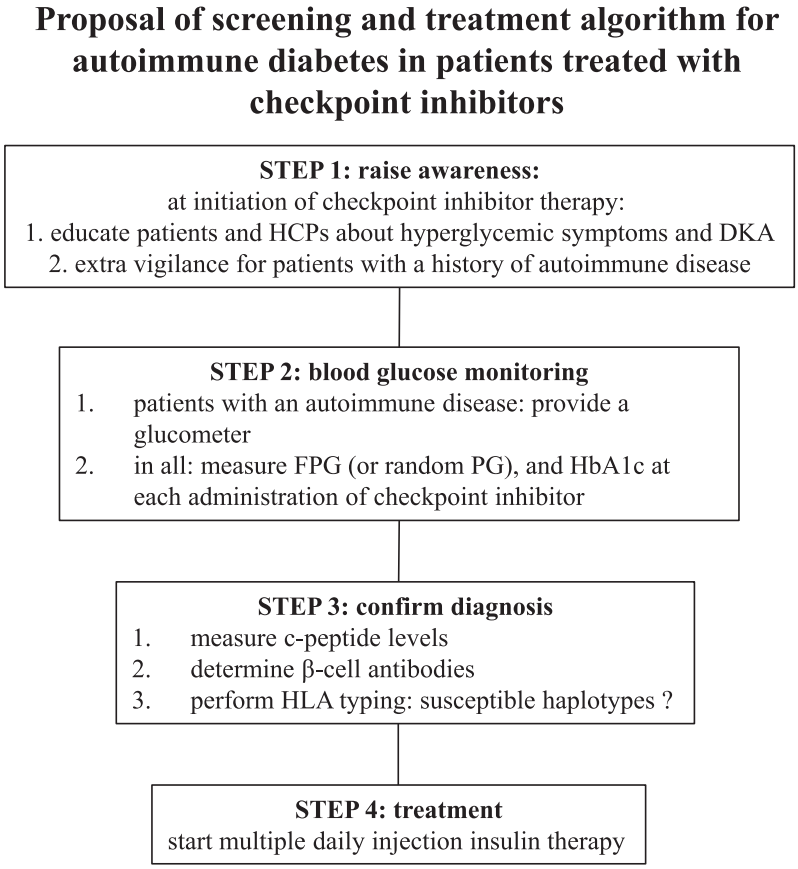

Figure 2. Proposal of screening and treatment algorithm for autoimmune diabetes in patients treated with checkpoint inhibitors. FPG, fasting plasma glucose; HCP, health care provider; PG, plasma glucose.

be aware of irAEs, including autoimmune diabetes mellitus and other endocrinopathies.

Despite the rarity of diabetes in this patient population, the field would benefit from a consensus research protocol according to which patients could be evaluated prior to therapy with checkpoint inhibitors and on follow-up. It would be ideal if this condition could be prevented, certainly considering the possible aggressive nature of this form of autoimmune diabetes. However, some authors argue that the knowledge of being vulnerable to certain irAEs may increase anxiety in patients, without changing management (37).

To diagnose autoimmune diabetes early, some authors recommend routine measurement of HbA_{1c} and blood glucose levels in patients, prior to the start of immunotherapy and while receiving immunotherapy. Other authors advise clinicians to educate their patients about symptoms of diabetes, DKA, and other irAEs (24). Furthermore, it is also suggested to provide patients with a device for capillary blood glucose monitoring (18). In our opinion, a combination of these (education, routine glucose measurements, and home blood glucose monitoring) should be used.

In clinical practice, we propose to educate all patients about hyperglycemic symptoms and DKA and to raise awareness in health care professionals. In patients with a history of autoimmune disease (*e.g.*, Hashimoto hypothyroiditis, Graves disease, pernicious anemia, celiac disease, *etc.*), we suggest providing a glucometer. In all patients, fasting or random plasma glucose and HbA_{1c} levels should also be tested at each administration of PD-1 inhibitor therapy. If positive, HLA type, C-peptide, and β-cell antibodies should be determined to confirm the diagnosis of type 1 diabetes. This approach (Fig. 2) should minimize long delays in diagnosis and help in avoiding the development of potentially life-threatening DKA. Furthermore, based on the information collected by this approach, in the future, the study of autoreactive T cells, HLA typing, and autoantibody testing, or even testing type 1 diabetes–associated single nucleotide polymorphisms to calculate genetic risk scores for type 1 diabetes may be feasible and help us to gain insight in the pathogenetic process of PD-1 inhibitor–induced type 1 diabetes mellitus.

Conclusion

Autoimmune diabetes induced by anti–PD-1 therapy is a rare but potentially life-threatening immune-related side effect. Because the use of immunotherapy is expected to increase, it is essential to raise awareness of DKA and to diagnose and treat this aggressive form of autoimmune diabetes in a timely fashion.

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