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Context: Pembrolizumab (Keytruda) 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 (irAE) 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 4 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 January 1, 2012 and January 1, 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 programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus to date, including a well-characterized novel case of islet cell antibody (ICA) and glutamic acid decarboxylase antibody (GADA) positive diabetes mellitus, in a patient with a diabetes prone HLA genotype. She presented with diabetic ketoacidosis (DKA) during pembrolizumab therapy for a metastatic uveal melanoma. Furthermore, we discuss potential pathogenic mechanisms, clinical presentation, prognostic markers (beta-cell antibodies, HLA type), a treatment and a screening protocol.
Conclusions: Since 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.

We reviewed the literature about programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus. Fasting or random plasma glucose and HbA1c levels should be tested at each administration.

Introduction

Cancer immunotherapy is a successful and fast growing field. Pembrolizumab (Keytruda) and nivolumab (Opdivo) are two IgG4 monoclonal antibodies targeting the programmed cell death-1 (PD-1) receptor (1-4). This receptor is important in maintaining self-tolerance and is therapeutically targeted by immune checkpoint inhibiting monoclonal antibodies (mAb) 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 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)).

Here, we provide an overview of all published cases (n=42) of programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus, including a new case that presented with diabetic ketoacidosis (DKA) during pembrolizumab therapy for a metastatic uveal melanoma. Furthermore, we discuss potential pathogenic mechanisms, clinical presentation, prognostic markers (beta-cell antibodies, 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,…) 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 anti-tumor immune response (3,4). However, when the PD1-pathway is blocked, not only T cells targeting cancer survive, but also autoreactive T cells such as those targeting pancreatic islet cells, 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, 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- programmed death 1 (PD-1) monoclonal antibodies (mAbs) like nivolumab

and pembrolizumab) can reinvigorate these exhausted T cells, resulting in better control of cancer (4,10).

Responders and non-responders 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 (TILs).

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 intra- and intertumor (primary vs metastatic) PD-L1 expression; location of signal (membrane, intracellular, 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 TILs 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 beta 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 non-obese 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 significant reduction in PD-1 expression in CD4(+) T cells compared to 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 auto-reactive 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 beta 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 beta 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 diabetes mellitus type 1.

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-FDG PET-CT).

In March 2017 she presented with right-sided abdominal pain due to new metastatic liver disease. Subsequently a treatment with Keytruda (pembrolizumab) was started. The patient was treated in compliance with the principles of the Declaration of Helsinki, the principles of Good Clinical Practice (GDP), and of General Data Protection Regulation (GDPR) and in accordance with all applicable regulatory and Ethics Committee requirements. She received 2 infusions of Pembrolizumab (2mg/kg q3w). Two weeks after the second infusion, she presented with complaints of anorexia, vomiting, polydipsia and headache at the emergency department. Diabetic ketoacidosis was diagnosed; she had a glycaemia 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 – 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 patients had a normal pituitary function (TSH 0.94 mU/l, FT4 16.2 pmol/l; prolactin 76.4 µg/l, FSH 47.3 U/l). MRI of the pituitary gland also revealed no abnormalities (no enhancement on T2-weighted images, no thickened pituitary stalk).

After a 24 hour stay in the intensive care unit being treated according to our hospital diabetic ketoacidosis protocol, the patient was transferred to the department of endocrinology under a low dose of continuous IV insulin. Further testing revealed a hemoglobin A1C 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 (ICA) of 400 JDF units (normal <12) and an elevated glutamic acid decarboxylase antibody (GADA) of 27,881 WHO U/ml (normal <23). Insulinoma antigen-2 antibodies (IA2A), 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 5 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 diabetic ketoacidosis. Diabetic ketoacidosis was the first sign of diabetes in 30 out of 35 (85.7%) cases reported with sufficient information about presentation. Two patients presented with ketonuria, but no ketoacidosis.

Time from initiation of anti-PD1 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 3 infusions or 6 weeks. Our patient developed DKA 2 weeks after the second infusion.

Auto-antibodies

Based on the 42 reported cases, there is no clear pattern of diabetes related autoantibodies. Approximately half of the tested cases (22/39 or 56%) had detectable diabetes related autoantibodies. In those 22 cases, glutamic acid decarboxylase antibodies (GADA) were positive in all subjects, tyrosine phosphatase autoantibodies (IA2A) in 4/20, ICA in only 2 patients, and insulin autoantibodies and ZnT8 antibodies in only one 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. 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, while others developed antibodies but did not develop diabetes (12).

Furthermore, it should be taken into account that, while 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. suggest that the interval from the start of treatment with anti-PD-1/PD-L1 antibodies and the onset of type 1 diabetes mellitus is related to the presence or absence of GADA (21). Their hypothesis was that GADA-positive patients developed type 1 diabetes mellitus earlier, in the first 2 months after the start of therapy, while GADA-negative patients developed type 1 diabetes mellitus later, after 2 months of therapy (21). In line with the observation of Usui et al., Gauci et al. found that the median interval from immunotherapy initiation to diagnosis of diabetes was 3 weeks in GADA positive cases versus 12.5 weeks in GADA negative cases (data from the 24 patients) (22). 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 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 cases versus 9 weeks in GADA negative cases (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 available. In the case report published by Lowe et al. 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 a case report of Gauci et al., retrospective investigations on serum of 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., diabetes related autoantibodies were already present prior to anti-PD1 therapy (24).

HbA1c and C-peptide

Serum C-peptide was low or undetectable at diagnosis or during follow-up in 30 of 32 tested patients. HbA1c levels vary within the reported cases; from 6.4% to 10.7% (46-93 mmol/mol). The low or undetectable C-peptide combined with the moderately low HbA1c 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 HbA1c 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 or not to start immune checkpoint inhibitor therapy in patients with a preexisting autoimmune disease will probably not be affected because the significant beneficial effects outweigh the disadvantages of irAEs.

Ten case reports mentioned thyroid disease (22,23,27-33). In our patient thyroid function was normal. Since our patient presented with vomiting and headache, other known irAE of anti-PD-1 therapy, such as hypophysitis and autoimmune adrenalitis (Addison's disease), needed to be investigated and were ruled out. In literature, two cases have been reported of

patients who developed hypophysitis and autoimmune diabetes mellitus during immune checkpoint inhibitor therapy (23,34). Addison's disease is known to occur in 0-8% of patients treated with anti-PD1 or anti-PDL1 therapy (1). However, this side effect was also not present in the 42 reported cases. Recently, the first case of central diabetes insipidus was reported (35).

Age of onset

In the 42 cases, the median age at diagnosis was 63 years (range 28-83). 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 (LADA). 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 human leucocyte antigen (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 a 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, 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. demonstrated that for a subset of non-melanoma patients treated with PD-1 checkpoint inhibitors, in particular those with low-grade immune-related adverse events, immune-related adverse events were predictive for an improved response rate and longer time to next therapy and longer survival (39). This confirmed the study of Freeman-Keller et al. who observed that cutaneous irAEs (rash and vitiligo) were associated with improved survival in melanoma patients treated with nivolumab. However, they observed no significant 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-alpha inhibitors, there is no treatment for autoimmune diabetes mellitus. One research group reported their attempt of treatment with oral prednisolone at 2 mg/kg for 3 days, 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 monoclonal antibodies, 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 80–95% of pancreatic β-cells have been destroyed. With such a significant loss of β cells, it seems unlikely that immunotherapy dose modification or immunosuppression with corticosteroids would alter the course of disease.

Currently, the treatment for immunotherapy induced diabetes and diabetic ketoacidosis 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 glycaemia was controlled. Restarting the immunotherapy did not cause a change in glycaemia, and the patients kept stable insulin requirements and fasting blood glucose levels. Also in our patient, resuming the check point inhibitor did not worsen glycemic control.

Proposal of a screening strategy

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

In order to diagnose autoimmune diabetes early, some authors recommend routine measurement of HbA1c 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 diabetic ketoacidosis and to raise awareness in health care professionals. In patients with a history of autoimmune disease (e.g. Hashimoto hypothyroiditis, Graves' disease, pernicious anaemia, coeliac disease, …) we suggest to provide a glucometer. In all patients, fasting or random plasma glucose and HbA1c levels should also be tested at each administration of PD1 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 (figure 2) should minimize long delays in diagnosis and help in avoiding the development of potentially life threatening diabetic ketoacidosis. 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 T1D-associated SNPs to calculate genetic risk scores for T1D may be feasible and help us to gain insight in the pathogenetic process of Programmed cell death-1 (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. Since the use of immunotherapy is expected to increase, it is essential to raise awareness of diabetic ketoacidosis and to timely diagnose and treat this aggressive form of autoimmune diabetes.

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Figure 1. Legend: 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. Similar to the mechanism in figure 1, pancreatic β cells express PD-L1 and thereby

evade 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.

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. Legend: 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. Similar to the mechanism in figure 1, pancreatic β cells express PD-L1 and thereby evade 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.

Figure 2. Legend: HCP = health care provider, DKA = diabetic ketoacidosis, HLA = Human leukocyte antigen, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin.

Figure 2. Proposal of screening and treatment algorithm for autoimmune diabetes in patients treated with checkpoint inhibitors.

Table 1. Reported cases (15,18,21-24,27-34,36-38,41-55)

Author, year	Sex	Age (years)	Malignancy	DKA	HbA1c	Therapy	Type 1 diabetes onset time (number of infusions)	Type 1 diabetes onset time (weeks)	Antibodies	C-peptide	Reference range C-peptide	HLA-typing
Brahmer et al., 2012	/	/	/	/	/	c	/	/	/	/	/	/
Gaudy et al., 2015	F	44	CM	+	6.8% (52 mmol/mol)	p	2	/	-	undetectable	/	NHR
Mellati et al., 2015	M	70	NSCLC	+	9.8% (84 mmol/mol)	c	5	15	-	0.3 ng/mL	1.0–7.1 ng/mL	/
Mellati et al., 2015	F	66	SSCC	+	9.4% (79 mmol/mol)	c	3	7	GAD+	<0.1 ng/mL	1.0–7.1 ng/mL	high risk: DR3-DQ2(HLA-DQB1*02)/DR4-DQ8
Martin-Liberal et al., 2015 Spain et al., 2016	F	54	CM	+	/	p	3	/	GAD+	/	/	high risk: DRB1*04 and DQB1*03:02 (HLA A2 DR4 DQ8)
Hughes et al., 2015	F	64	CM	‡	7.4% (57 mmol/mol)	p	/	4	-	0.5 ng/mL	1.1–4.4 ng/mL	high risk: DR4+
Hughes et al., 2015	F	55	CM	+	6.9% (52 mmol/mol)	n	/	20	/	<0.1 ng/dL	1.1–4.4 ng/mL	high risk: A2.I +, DR4+
Hughes et al., 2015	F	83	NSCLC	+	7.7% (61 mmol/mol)	n	/	4	GAD+	<0.1 ng/dL	1.1–4.4 ng/mL	high risk: A2.I +, DR4+
Hughes et al., 2015	M	63	RCC	-	8.2% (66 mmol/mol)	n	/	16	GAD+, ICA+, IAA+	1.3 ng/dL	1.1–4.4 ng/mL	high risk: A2.I +, DR4+
Hughes et al., 2015	M	58	SCLC	+	9.7% (83 mmol/mol)	n	/	1	GAD+	<0.1 ng/dL	1.1–4.4 ng/mL	high risk: A2.I +
Hansen et al., 2016	M	58	CM	/	9.7% (83 mmol/mol)	p	17	52	GAD+	2.4 ng/mL	/	/
Teramoto et al., 2016	F	63	CM	+	8.9% (74 mmol/mol)	n	8	/	-	0.08 ng/mL	/	/

Humayun et al., 2016	M	55	CM	+	10.7% (93 mmol/mol)	p	9	/	-	/	/	/
Miyoshi et al., 2016	F	66	CM	+	<8.7% (<72 mmol/mol)	n	6	17	-	0.23 ng/mL	0.8-2.3 ng/mL	NHR
Okamoto et al., 2016	F	55	CM	‡	7.0% (53 mmol/mol)	n	/	52	-	<0.1 ng/mL	0.61–2.09 ng/mL	high risk: DRB1*04:05-DQB1*04:01
Aleksova et al., 2016	M	60	CM	+	7.1% (54 mmol/mol)	p	2	5	-	57 pmol/L	300–2350 pmol/L	/
Chae et al., 2016	M	76	NSCLC	-	5.8% (40 mmol/mol)	p	2	/	GAD+, IA2A+	0.81 ng/mL	0.9–3.85 ng/mL	/
Lowe et al., 2016	M	54	CM	+	/	n + i	3	/	GAD+	<0.1 ng/mL	/	NHR
Hofmann et al., 2016	F	58	CM	/	/	p	1	3	GAD+	low	/	/
Hofmann et al., 2016	F	70	CM	/	/	n	4	6	-	<16 pmol/L	140-830 pmol/L	/
Hofmann et al., 2016	F	78	CM	+	/	n	2	3	GAD+	low	/	/
Hofmann et al., 2016	M	40	/	/	/	n	/	6	/	/	/	/
Alhusseini et al., 2016	M	56	NSCLC	+	8.5% (69 mmol/mol)	p + i	1	3	GAD+, IA2A+	undetectable	/	/
Hao et al., 2016/2017	F	28	CM	+	/	n	3	/	GAD+	/	/	high risk: DR3 DQ3
Shah et al., 2016	F	77	NSCLC	+	10.2% (88 mmol/mol)	n	1	2	-	0.81 ng/mL	/	NHR
Farrell et al., 2017	M	30	CM	+	7.4% (57 mmol/mol)	p	/	/	-	undetectable	/	/
Thoreau et al., 2017	M	73	CM	+	8.5% (69 mmol/mol)	p	/	26	-	/	/	/
Godwin et al., 2017	F	34	NSCLC	+	7.1% (54 mmol/mol)	n	2	/	GAD+	<0.1 ng/mL	0.8–3.85 ng/mL	NHR
Usui et al., 2017	M	31	NSCLC	+	6.4% (46 mmol/mol)	n	1	2	GAD+	<0.03 ng/mL	>0.03 ng/mL	high risk: DRB1*04:05-DQB1*04:01
Usui et al., 2017	F	62	NSCLC	/	6.5% (48 mmol/mol)	n	4	/	-	/	/	high risk: DRB1*09:01-DQB1*03:03
Munakata et al., 2017	M	72	HL	-	7.3% (56 mmol/mol)	n	5	/	-	/	/	/
Alzenaidi et al., 2017	M	46	CM	+	8.0% (64 mmol/mol)	n + i	2	/	GAD+	0.2 ng/mL	0.9-5.5 ng/mL	/
Ishikawa et al., 2017	F	54	CM	/	7.0% (53 mmol/mol)	n	16	/	-	<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
Leonardi et al., 2017	M	66	NSCLC	+	7.6% (60 mmol/mol)	p	3	/	GAD+	0.3 ng/mL	1.1–4.4 ng/mL	/
Li et al., 2017	M	63	NSCLC	+	7.2% (55 mmol/mol)	n	/	4	GAD+	/	/	/
Gauci et al., 2017	M	73	CM	+	8.8% (73 mmol/mol)	n	3	6	GAD+, ZnT8A+	0 nmol/L	0.5 ng/mL	/
Scott et al., 2017	M	58	/	+	6.8% (50 mmol/mol)	p + i	3	9	-	/	/	/
Kapke et al., 2017	M	83	SCC	+	7.4% (57 mmol/mol)	n	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

Kapke et al., 2017	F	63	UC	+	7.8% (61 mmol/mol)	a	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
Araujo et al., 2017	F	73	NSCLC	+	7.2% (55 mmol/mol)	n	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
Zaied et al., 2018	M	+-70	RCC	+	8.4% (68 mmol/mol)	n	3	6	-	0.4 ng/mL	1.1-4.4 ng/mL	/
Current patient	F	73	UM	+	7.1% (54 mmol/mol)	p	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

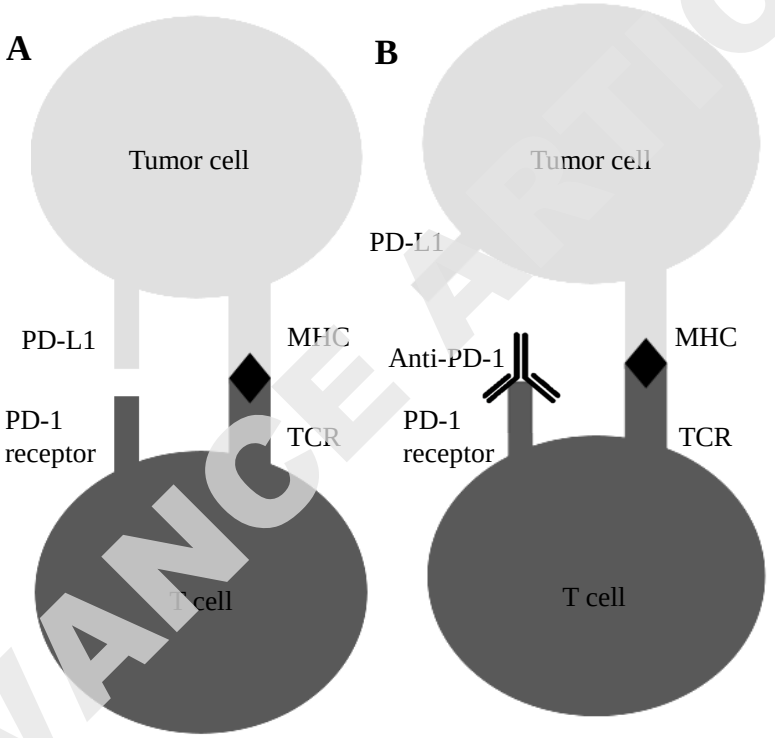
Table legend: DKA = diabetic ketoacidosis, HbA1c = glycated haemoglobin, HLA = Human leukocyte antigen, / = not reported, c = not-specified anti-PDL1-antibody, CM = cutaneous melanoma, + = positive, p = pembrolizumab, - = negative, NHR = no high risk type, NSCLC = non-small cell lung cancer, SSCC = Sarcomatoid squamous cell carcinoma, GAD = glutamic acid decarboxylase antibody, ‡ = ketonuria, n = nivolumab, RCC = renal cell carcinoma, ICA = islet cell antibody, IAA = insulin autoantibody, SCLC = small cell lung cancer, IA2A = Islet antigen 2 antibody, i = ipilimumab, HL = Hodgkin lymphoma, ZnT8A = Zinc transporter 8 antibody, SCC = squamous cell carcinoma, a = atezolizumab, UC = urothelial carcinoma of the bladder, UM = uveal melanoma.
Note: HLA information is not consistently presented in terms of nomenclature, or alleles reported, because of limitation of what was reported in literature.

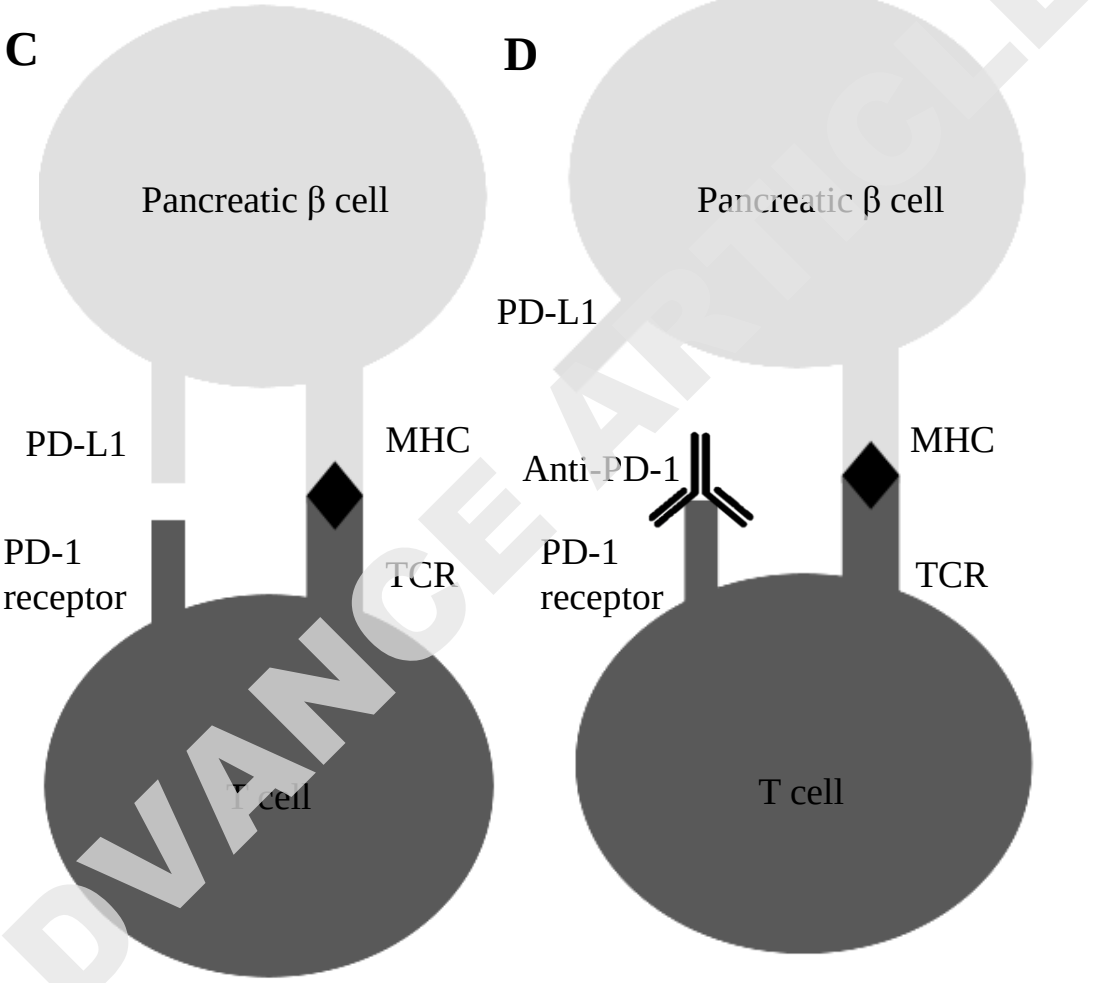
Table 2. Characteristics of reported patients with immunotherapy associated type 1 diabetes

Reported cases:	42
Causative agent	
Nivolumab	21
Pembrolizumab	12
Nivolumab + ipilimumab	2
Anti-PDL1	2
Anti-PD1	1
Pembrolizumab + ipilimumab	2
Azetolizumab	1
Demographic data	
Sex (men/women/not reported)	21/20/1
Age (years)	63 (28-83)
Presentation	
Diabetic ketoacidosis	30 (71.4%)
Hyperglycemia (negative for DKA)	3
HbA1c (%)	7.5 (6.4-10.7)
HbA1c (mmol/mol)	58.5 (46-93)
Time of diagnosis after start of immunotherapy	
Number of doses	3 (1-17)
Onset in weeks	6 (1 -52)
Beta cell antibodies	
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 auto-immune disease	12/42 (28.6%)

Table legend: DKA = Diabetic ketoacidosis, HbA1c = Glycated hemoglobin, HLA = Human leucocyte antigen, GAD =Glutamic acid decarboxylase antibody, IA2A = Insulinoma antigen-2 antibody, ICA = Islet cell antibody, IAA = insulin autoantibody, ZnT8A = Zinc transporter 8 antibody, HLA = Human leukocyte antigen

Data are median (range) or number (%)





Proposal of screening and treatment algorithm for autoimmune diabetes in patients treated with checkpoint inhibitors