Cancer Immunol Immunother (2017) 66:1399–1410
DOI 10.1007/s00262-017-2033-8

ORIGINAL ARTICLE

Autoimmune diabetes induced by PD-1 inhibitor—retrospective analysis and pathogenesis: a case report and literature review

Marie-Léa Gauci[1,2] · Pauline Laly[1,2] · Tiphaine Vidal-Trecan[5,6] · Barouyr Baroudjian[1,2] · Jérémy Gottlieb[1,2] · Nika Madjlessi-Ezra[1,2] · Laetitia Da Meda[1,2] · Isabelle Madelaine-Chambrin[2,7] · Martine Bagot[1,2] · Nicole Basset-Seguin[1,2] · Cécile Pages[1,2] · Samia Mourah[2,8] · Philippe Boudou[3,4] · Céleste Lebbé[1,2] · Jean-François Gautier[5,6]

Received: 25 January 2017 / Accepted: 12 June 2017 / Published online: 20 June 2017

Abstract Anti-PD-1 antibody treatment is approved in advanced melanoma and provides median overall survival over 24 months. The main treatment-related side effects are immune-related adverse events, which include rash, pruritus, vitiligo, thyroiditis, diarrhoea, hepatitis and pneumonitis. We report a case of autoimmune diabetes related to nivolumab treatment. A 73-year-old man was treated in second line with nivolumab at 3 mg/kg every two weeks for metastatic melanoma. At 6 weeks of treatment, he displayed diabetic ketoacidosis. Nivolumab was withheld 3.5 weeks and insulin therapy was initiated, enabling a normalization of glycaemia and the disappearance of symptoms. Laboratory investigations demonstrated the presence of islet cell autoantibodies, while C-peptide was undetectable. Retrospective explorations on serum banked at week 0 and 3 months before the start of nivolumab, already showed the presence of autoantibodies, but normal insulin, C-peptide secretion and glycaemia. Partial response was obtained at month 3, and nivolumab was then resumed at the same dose. The clinical context and biological investigations before, at and after nivolumab initiation suggest the autoimmune origin of this diabetes, most likely induced by anti-PD-1 antibody in a predisposed patient. The role of PD-1/PD-L1 binding is well known in the pathogenesis of type 1 diabetes. Therefore, this rare side effect can be expected in a context of anti-PD-1 treatment. Glycaemia should be monitored during PD-1/PD-L1 blockade. The presence of autoantibodies before treatment could identify individuals at risk of developing diabetes, but systematic titration may not be relevant considering the rarity of this side effect.

Keywords Melanoma · Anti-PD-1 antibody · Autoimmune diabetes · Adverse events

Abbreviations

BMS	Bristol–Myers Squibb
BRAF	Murine sarcoma viral oncogene homolog B1
GADA	Glutamic acid decarboxylase antibody
HbA1c	Glycated haemoglobin Insulinoma antigen-2 antibody
IA2A	Insulinoma antigen-2 antibody
MEK	Mitogen activated protein kinase kinase
NOD	Non-obese diabetic
ZnT8A	Zinc transporter 8 antibody

Philippe Boudou, Céleste Lebbé and Jean-François Gautier are co-last authors.

✉ Marie-Léa Gauci
marie-lea.gauci@hotmail.fr

1 AP-HP Dermatology Department, Saint-Louis Hospital, 1 avenue Claude Vellefaux, 75475 Paris Cedex 10, France

2 INSERM U976, Université Paris Diderot-Paris VII, Sorbonne Paris Cité, Paris, France

3 AP-HP Hormonology Department, Saint-Louis Hospital, Paris, France

4 Université Paris Diderot-Paris VII, Sorbonne Paris Cité, Paris, France

5 AP-HP Diabetology Department, Lariboisière Hospital, Paris, France

6 INSERM U1138, Université Paris Diderot-Paris VII, Sorbonne Paris Cité, Paris, France

7 AP-HP Pharmacology Department, Saint-Louis Hospital, Paris, France

8 AP-HP Pharmacogenomic Laboratory, Saint-Louis Hospital, Paris, France

Introduction

Nivolumab is an immune-checkpoint inhibitor antibody (anti-PD-1 antibody) that selectively blocks the interaction of the PD-1 receptor, on the T cells, with its two known programmed death ligands, PD-L1 and PD-L2, present on the surface of the tumour cells and immune cells in the tumour micro-environment. It thus restores T cell activation and proliferation and consequently induces an anti-tumour immune response. This induces a decrease in peripheral immune tolerance, which leads to T lymphocyte autoimmune clone activation. Nivolumab is associated with significant improvement in overall survival compared to the former first-line chemotherapy using dacarbazine [1] and was approved by the Food and Drug Administration for the treatment of advanced melanoma in September 2014 and by European Medicines Agency (EMA) in Europe in June 2015. The main side effects of anti-PD-1 therapy are immune-related and include rash, pruritus, vitiligo, thyroiditis, diarrhoea, hepatitis and pneumonitis. Cases of autoimmune diabetes induced by immunotherapy are infrequent and poorly described. We describe islet beta-cell antibody positivity, highlighted retrospectively, in a new case of autoimmune diabetes induced by nivolumab.

Case report

In 2011, a 73-year-old man, with a body mass index of 28 kg/m^2, a history of dyslipidemia, and no personal or family history of diabetes, underwent surgical excision of a 2.65-mm-thick, ulcerated, BRAF-mutated, cutaneous melanoma on the back, with negative sentinel lymph nodes. He received low-dose alpha interferon (IFNα) adjuvant therapy for 10 months until the occurrence of Graves' disease, treated with carbimazole for 1 year. In July 2015, he developed stage IV M1c metastatic melanoma and was treated first line with the vemurafenib (BRAF inhibitor) and cobimetinib (MEK inhibitor) combination. At 3 months, the disease had progressed per RECIST, and a second-line treatment with nivolumab 3 mg/kg every two weeks was introduced. At 6 weeks of nivolumab, before the fourth infusion, the patient suddenly complained of abdominal pain, vomiting and severe asthenia associated with a polyuria–polydipsia syndrome. He was admitted to the emergency unit of the hospital. The initial biological investigation evidenced the following: glycaemia: 27.78 mmol/l, urinary dipstick test: 3 crosses of glucose and ketone, creatinine: 177 µmol/l (baseline: 90 µmol/l), bicarbonate: 18 mmol/l and glycated haemoglobin (HbA1c): 8.8% (normal range 4–6%). These data were consistent with type 1 diabetes onset with acute functional renal failure. Insulin therapy was initiated with gradually increasing doses, providing a normalization of glycaemia and clinical features. Extended biological investigations revealed anti-glutamic acid decarboxylase antibody (GADA) > 2000 IU/L, zinc transporter 8 antibody (ZnT8A) at 802U/ml, (protein phosphatase-like) and insulinoma antigen-2 antibody (IA2A) at 27 U/ml. C-peptide was undetectable. Retrospective investigations based on frozen serum (week 0 (T0) and 3 months before starting nivolumab treatment (T-3 m)) already showed positivity for autoantibodies (Fig. 1). At this time, insulin and C-peptide concentrations and glycaemia were normal (Fig. 2). Nivolumab was resumed at the same dose after three and a half weeks without affecting glycaemia. Tumour assessment 3 months after nivolumab introduction showed complete metabolic response on positron emission tomography/computed tomography).

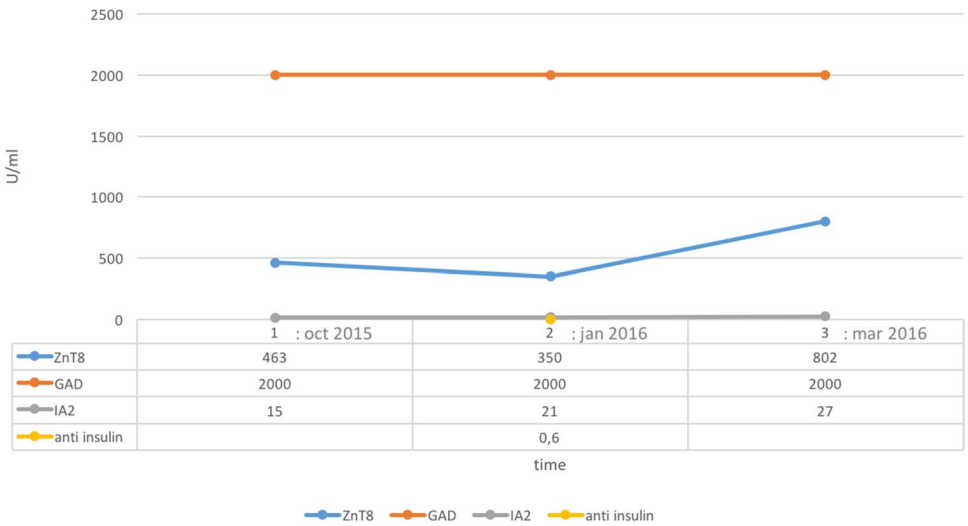

Fig. 1 Autoantibody evolution: before, at the time of and after nivolumab treatment. These data show autoantibody presence before anti-PD-1 treatment and symptom appearance. *IA2* insulinoma antigen-2, *ZnT8* zinc transporter 8, *GAD* glutamic acid decarboxylase

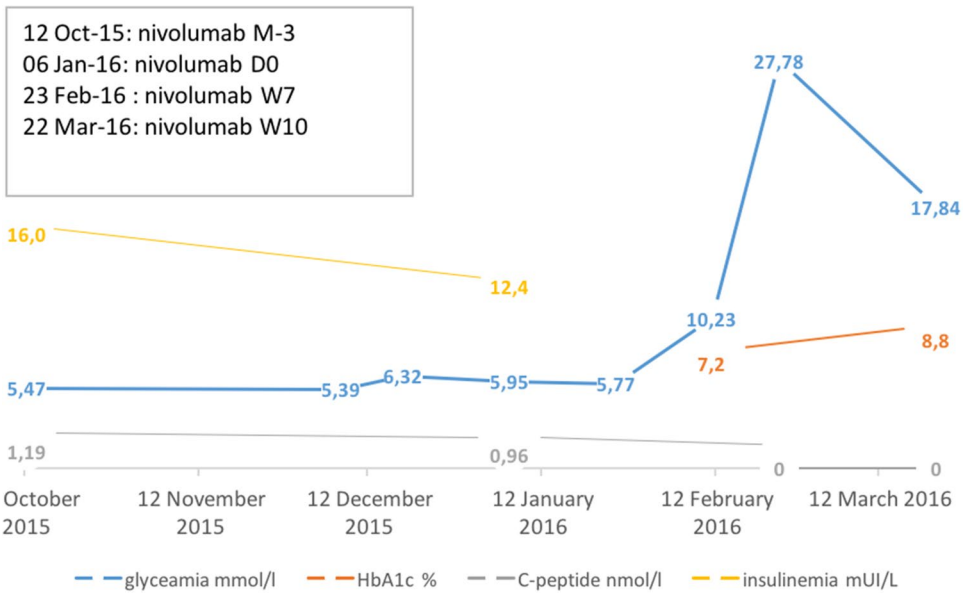

Fig. 2 Glycaemia, HbA1c, C-peptide level and insulinemia evolution over time. These data describe biological and kinetic parameters of diabetes onset. *M* month, *W* week, *D* day

Discussion

The presence of islet beta-cell-related autoantibodies at diabetes onset, possibly reinforced by their triple positivity (although no data are available in this type of population), supports the diagnosis of autoimmune type 1A diabetes. The patient had already displayed autoimmune hyperthyroidism under IFNα therapy, which could have triggered the appearance of beta-cell antibodies. However, the occurrence of ketoacidosis in a patient presenting with hyperglycaemic symptoms for less than 2 weeks and the moderate rise in HbA1c level, indicate recent glycaemic failure, as observed in fulminant diabetes. Thus, diabetes onset in this patient could be related to treatment with anti-PD-1 antibody in a predisposed subject.

Blockade of PD-1 or its ligand, PD-L1, rapidly precipitates diabetes in pre-diabetic non-obese diabetic (NOD) mice [2]. In addition, selective PD-L1 deficiency in pancreatic cells and deficiency or blockade of PD-1 on T cells activate specific CD8 T cells, leading to diabetes in wild-type mice [3]. The rapid onset of diabetes in our patient was probably due to an autoaggressive effector CD8+ T cell clone that was suddenly set free when PD-1 was blocked. Indeed, PD-1 binding to PD-L1 can down-regulate the diabetogenic potential of specific CD8 T cells [3]. In addition, Indira Guleria et al. [4] showed that CD8+ T cells accumulate in the pancreas of PD-L1/PD-L2-deficient NOD mice compared with wild-type NOD controls, inducing an autoimmune response against pancreatic beta-cells and rapid destruction of beta islet cells [4].

Twenty-four [5–19] cases of diabetes have already been reported as a side effect of anti-PD-1/PD-L1 antibody treatment (Table 1). Of these cases, only one was related to anti-PD-L1 therapy [10], seven (29%) patients were treated with pembrolizumab [5, 6, 8, 9, 14, 15, 18], 13 (54%) patients were treated with nivolumab [8, 10–14, 17, 19], and for one case, the specific anti-PD-1 treatment was not named [7]. Two patients were treated with combined therapy (nivolumab associated with ipilimumab) [8, 16].

These 24 cases of diabetes related to anti-PD-1/PD-L1 therapy occurred between 1 week and 12 months after initiation (median 8.5 weeks). At diabetes onset, ketoacidosis was reported in 18 (75%) out of the 24 patients [5–9, 11–17]. All these patients had moderate increases in HbA1c level. Ten (42%) patients presented abnormally low HbA1c, under 8.7%, contrasting with their hyperglycaemia [8–10, 12, 13, 17], alongside low or undetectable C-peptide level, which reflects rapid onset as described in fulminant diabetes.

Fulminant diabetes is a subtype of type 1 diabetes discovered in Japan [20] and has been reported in Asia, Polynesia but rather rarely in Europe [21]. It is defined as diabetes in which the process of beta-cell destruction and the progression of hyperglycaemia and ketoacidosis are extremely rapid. The pathogenesis of this disease remains to be clarified, but the involvement of human leucocyte antigen (HLA DRB1*04:05-DQB1*04:01) genes and viruses has been suggested. The hyperglycaemic symptoms last a few days. There is a high prevalence of preceding common-cold-like and gastrointestinal symptoms and an unexpectedly near-normal or moderately increased level of HbA1c, contrasting with the very high plasma glucose levels associated with ketoacidosis. C-peptide concentrations and type 1 diabetes autoantibody are usually not detectable [22]. However, in most cases, islet T lymphocyte infiltration has been observed. In our patient, the short duration of

Table 1 Literature review

Authors	Age (year-old)	Gender	Neoplasia	IFN adjuvant therapy	Line	Treatment	Other immune-related side effect	Time to onset weeks	Symptoms	HbA1c at diagnosis (%)	Glycaemia (mmol/l)	Ketoacidosis
Hansen et al. [5]	58	Man	BRAF V600E-mutated melanoma	Yes	4th after vemurafenib, high-dose IL2 and ipilimumab	Pembrolizumab	Hypothyroidism Vitiligo Fatigue	48	Fungal inguinal rash, fatigue, weight loss, polydipsia, polyuria no abdominal pain or symptoms of pancreatic enzyme deficiency	9.7	22.22	Yes
Martin-Liberal et al. [6]	54	Woman	BRAF WT melanoma	No	2nd after ipilimumab	Pembrolizumab	N/A	9	Lethargy, vomiting, polydipsia and polyuria	N/A	N/A	Yes
Mellati et al. [7]	70	Man	Adenocarcinoma of the lung	No	N/A	Anti-PDL-1 (name unknown)	no	15	N/A	9.8	22.33	Yes
	66	Woman	Sarcomatoid squamous cell carcinoma of the jaw	No	N/A	Anti-PD-1 (name unknown)	Hypothyroidism	7	N/A	9.4	41.77	Yes

Table 1 continued

Authors	Age (year-old)	Gender	Neoplasia	IFN adjuvant therapy	Line	Treatment	Other immune-related side effect	Time to onset weeks	Symptoms	HbA1c at diagnosis (%)	Glycaemia (mmol/l)	Ketoacidosis
Hughes et al. [8]––	55	Woman	Melanoma	N/A	1st	Nivolumab + ipilimumab	Autoimmune thyroid disease	20	N/A	6.9	27.78	Yes
	83	Woman	Non-small cell lung cancer	N/A	N/A	Nivolumab	no	4	N/A	7.7	16.67	Yes
	63	Man	Renal cell carcinoma with pancreatic metastasis	N/A	4th after Proleukin, bevacizumab and interferon	Nivolumab	no	16	N/A	8.2	11.10	No
	58	Man	Small cell lung cancer	N/A	3rd after Carboplatin, etoposide, paclitaxel	Nivolumab	no	1	N/A	9.7	39.89	Yes
	64	Woman	Melanoma	N/A	1st	Pembrolizumab	Autoimmune thyroid disease, psoriasis	4	N/A	7.4	38.00	No
Gaudy et al. [9]	44	Woman	Melanoma	N/A	N/A	Pembrolizumab	N/A	8	Vomiting and confusion, with polyuria, polydipsia and a very recent weight loss (15 days)	6.85	50.45	Yes

Table 1 continued

Authors	Age (year-old)	Gender	Neoplasia	IFN adjuvant therapy	Line	Treatment	Other immune-related side effect	Time to onset weeks	Symptoms	HbA1c at diagnosis (%)	Glycaemia (mmol/l)	Ketoacidosis
Munakata et al. [10]	72	Man	Classic Hodgkin's lymphoma	No	3rd after six cycles of doxo-rubicin, bleomycin, vinblas-tine, and dacar-bazine (ABVD) and bren-tuximab vedotin monother-apy as the second-line treatment	Nivolumab	N/A	10	Slight thirst, polyuria and gen-eral fatigue	7.3	20.81	No
Teramoto et al. [11]	63	Woman	Vulvar mela-noma	No	2nd line after dacar-bazine	Nivolumab	N/A	30	General fatigue, polyuria and poly-dipsia	8.9	36.69	Yes
Miyoshi et al. [12]	66	Woman	Melanoma	No	Adjuvant therapy	Nivolumab	N/A	15	Diarrhoea and weight loss, anorexia, nausea, vomiting	7.3	29.47	Yes
Okamoto et al. [13]	55	Woman	Melanoma	No	4th after dac-arbazine, nimustine, cisplatin	Nivolumab	N/A	48	N/A	7	32.19	yes
Hofmann et al. [14]	70	Woman	Melanoma	No	1st	Nivolumab	Hyperthy-roidism	N/A	N/A	N/A	N/A	Yes
	78	Woman	Melanoma	No	2nd line after ipilimumab	Nivolumab	N/A	2	Vomiting, diarrhoea	N/A	N/A	Yes
	58	Woman	Melanoma	No	2nd line after ipilimumab	Pembrolizumab	N/A	3	Increased thirst and a persistent urge to urinate	N/A	N/A	Yes

Table 1 continued

Authors	Age (year-old)	Gender	Neoplasia	IFN adjuvant therapy	Line	Treatment	Other immune-related side effect	Time to onset weeks	Symptoms	HbA1c at diagnosis (%)	Glycaemia (mmol/l)	Ketoacidosis
	40	Man	Melanoma	No	4th after dacarbazine; polychemotherapy; ipilimumab	Nivolumab	Hypothyroidism	6	N/A	N/A	N/A	Yes
Aleksova et al. [15]	60	Man	Melanoma	N/A	2nd after ipilimumab	Pembrolizumab	N/A	5	N/A	N/A	27	Yes
Lowe et al. [16]	54	Man	Melanoma	No	1st	Nivolumab + ipilimumab	Autoimmune thyroiditis, hepatitis, colitis and adrenal insufficiency	31	Weakness, myalgia, nausea and vomiting	N/A	N/A	Yes
Usui et al. [17]	31	Man	Non-small cell lung cancer	No	3rd	Nivolumab	N/A	2	Fatigue and nausea	6.4	38.39	Yes
	62	Woman	Non-small cell lung cancer	No	3rd	Nivolumab	N/A	10	Thirst and polyuria	6.5	11.11	N/A
Chae et al. [18]	76	Man	Adenocarcinoma of the lung	No	1st	Pembrolizumab in combination with systemic chemotherapy (carboplatin, and nab-paclitaxel)	N/A	3	Asymptomatic	N/A	33.33	No
Ishikawa et al. [19]	No available data					Nivolumab						

Table 1 continued

Authors	Lipasemia (UI/L)	Autoantibodies GAD/IA2/ZnT8/anti Insulin	C-peptide (ng/ml) N > 0.5	HLA	Anti-PD1 therapy management	Toxicity evolution
Hansen et al. [5]	N	+/−/−/−	N/A	N/A	Pembrolizumab maintained with no rechallenge due to disease progression	Subcutaneous insulin regimen administered enabling glycaemia control Reversible diabetes after anti-PD1 discontinuation: by day 54 after onset of insulin-dependent diabetes, the patient was able to discontinue insulin with glycaemic, C-Peptide and HbA1C level normalization
Martin-Liberal et al. [6]	N/A	+/−/−/+	N/A	DRB1*04, DQB1*0302 (HLA A2 DR4 DQ8)	Pembrolizumab was not discontinued At the time of writing, two further cycles of pembrolizumab had been given without further toxicity and without changes in insulin requirements	Intravenous insulin initiated and then, switched to a subcutaneous regimen, providing satisfactory glucose levels after a 3-day admission Toxicity non-resolved
Mellati et al. [7]	N/A	−/N/A/N/A/−	0.3	N/A	No information about anti-PD-1 management Died from his advanced cancer 7 months later	Intravenous insulin initiated and then switched to a subcutaneous regimen, providing satisfactory glucose levels after a 3-day admission Toxicity non-resolved
	N/A	+/+/−/−/+	<0.1	DR3-DQ2/DR4-DQ8	Evolution not reported Toxicity non-resolved	
Hughes et al. [8]—	N/A	−/−/−/−	<0.1	A2.11, DR41	Insulin treatment initiated but no data about anti-PD-1 management	
	N/A	+/−/N/A/−	<0.1	A2.11, DR41		
	N/A	+/N/A/N/A/+	1.3	A2.11, DR41		
	N/A	+/N/A/N/A/−	<0.1	A2.11		
	N/A	−/N/A/N/A/−	0.5	DR41		
Gaudy et al. [9]	NCS increase	−/−/N/A/N/A	<0.1	N/A	Pembrolizumab was stopped and reintroduced with no further adverse event	Insulin therapy was required to control glycaemia Toxicity non-resolved

Table 1 continued

Authors	Lipasemia (UI/L)	Autoantibodies GAD/IA2/ZnT8/anti Insulin	C-peptide (ng/ml) N > 0.5	HLA	Anti-PD1 therapy management	Toxicity evolution
Munakata et al. [10]	Increased with diffuse pancreatic inflammation (MRI)	−/−/−/N/A	N/A	HLA-B*4002	Nivolumab was re-administered after glycaemia control without further hyperglycaemia	Long-term insulin replacement therapy was necessary It was treated 4 months more without recovery of endogenous insulin secretion Toxicity non-resolved
Teramoto et al. [11]	N/A	−/−/−/N/A	<0.1	N/A	Treatment stopped 6 weeks before diabetes appearance because of disease progression then, type 1 fulminant diabetes	Insulin therapy was started, enabling glycaemia control Toxicity non-resolved
Miyoshi et al. [12]	NCS increase	−/−/−/N/A	0.23	N/A	Nivolumab administration was continued (two doses).	Diabetes was controlled with basal-bolus insulin therapy Toxicity non-resolved
Okamoto et al. [13]	N	−/−/−/−	1	DRB1*04:05-DQB1*04:01	Nivolumab treatment was resumed 1 month after the patient's referral, and no further side effects were observed	Diabetes required insulin therapy Toxicity non-resolved
Hofmann et al. [14]	N/A	−/−/N/A/N/A	<0.1	N/A	Nivolumab was continued with good tumour response	Insulin therapy was needed to control glycaemia Toxicity non-resolved
	N/A	+/−/N/A/N/A	Low	N/A	No information about nivolumab management	Diabetes control with insulin therapy Toxicity non-resolved
	N/A	+/−/N/A/N/A	Low	N/A	2nd infusion of pembrolizumab was maintained until glycaemia normalization	Insulin therapy was administered Toxicity non-resolved
	N/A	N/A/N/A/N/A/N/A	N/A	N/A	N/A	
Aleksova et al. [15]	N/A	−/N/A/−/N/A	Low	N/A	No information about pembrolizumab management	Standard immunosuppression for irAEs was started using prednisolone in an attempt to salvage β-cell function but was unsuccessful Toxicity non-resolved

Table 1 continued

Authors	Lipasemia (UI/L)	Autoantibodies GAD/IA2/ZnT8/anti Insulin	C-peptide (ng/ml) N > 0.5	HLA	Anti-PD1 therapy management	Toxicity evolution
Lowe et al. [16]	N/A	+(undetectable 1 month prior)/N/A/N/A/N/A	<0.1		Patient was removed from the study and placed on surveillance	Intravenous fluids, insulin and methylprednisolone were initiated first (due to concomitant adrenal insufficiency). After immunotherapy discontinuation, continued insulin regimen with undetectable C-peptide level
Usui et al. [17]	N/A	+/N/A/N/A/N/A	<0.1	DRB1* 04:05-DQB1*04:01	Nivolumab was stopped during hyperglycaemia period	Insulin infusion but no data about evolution
	N/A	−/N/A/N/A/N/A	N/A	DRB1*09:01-DQB1* 03:03		Insulin therapy
Chae et al. [18]	N/A	+/+/N/A/N/A	0.81	Not performed	Following rapid correction and control with insulin, it was thought safe to proceed with continued pembrolizumab treatment was seen in the patient's glycaemic control	Empirical trial with prednisone at 10 mg per day, stopped after 25 days when no improvement Glycaemia was controlled with insulin therapy
Ishikawa et al. [19]					No available data	

N normal, *N/A* no available, *NCS* not clinically significant, − negative result, + positive result, *IA2* insulinoma antigen-2, *ZnT8* zinc transporter 8, *GAD* glutamic acid decarboxylase

symptoms, abdominal pain, the modest rise in HbA1c level in the presence of ketoacidosis and undetectable C-peptide (while normal a few weeks before) are in favour of fulminant diabetes despite type 1 autoantibody positivity.

In contrast, 6 out of the 24 reported patients [5, 7, 8, 11] had slower onset and higher HbA1c at diagnosis. For eight patients, no information was available on the means by which diabetes was diagnosed.

Five reported cases presented at least one other immune-related side effect [5, 7, 8, 16]: all presented thyroiditis, and three presented other side effects—psoriasis [8] for one, vitiligo [5] for another and the third, who was under combination therapy, presented multiple immune-related side effects including autoimmune hepatitis, colitis and adrenal insufficiency.

Autoantibodies were positive for only 11/22 (50%) [5–8, 14, 16–18] of the patients tested. Among the autoantibody-negative patients [7–15, 17], five were Japanese [10–13, 17], a population prone to fulminant diabetes. As suspected by Usui et al. [17], we also found that the time lapse from the start of treatment with anti-PD-1/PD-L1 antibodies to the onset of autoimmune diabetes appeared to be related to the presence or absence of GADA. The median time lapse from immunotherapy initiation to diabetes onset was, respectively, 3 weeks in the presence of GADA versus 12.5 weeks without (data from the 24 patients).

Here, we present a retrospective investigation study showing the positivity of autoantibodies in a case of autoimmune diabetes appearing after anti-PD-1 treatment, possibly previously triggered by IFNα therapy. As observed in children suffering from autoimmune diabetes, this could reflect subclinical disease before diabetes onset (beta-cell destruction by a specific TCD8+ cell clone without insulinopenia), but these antibodies have no pathogenic role. In some cases, they could provide a predictive factor for disease onset prior to the onset of symptoms and a prognostic factor for the course and control of the diabetes [23]. Additionally, the time from immunotherapy initiation and autoimmune diabetes development could be related to the presence of the autoantibodies. Thus, the predictive value of autoantibody positivity in patients exposed to anti-PD-1 agents for development of diabetes requires further study.

In the case reported by Lowe et al. [16] involving combination therapy (nivolumab plus ipilimumab), antibodies measured retrospectively at the start of immunotherapy were negative and appeared with the diabetes symptoms and glycaemia increase. In fact, data from the literature on NOD mice suggest that in the absence of negative co-stimulation by the PD-1/PD-L1 pathway, CTLA-4 possibly maintains the self-tolerance through IL-2, which stimulates T regulator cells [24]. CTLA-4 expression was also reported in one study to be significantly lower in patients with fulminant type 1 diabetes [25]. The rapid development of this autoimmune toxicity resulting from two immune-checkpoint blockades (CTLA-4 and PD-1) could sidestep the first phase when antibodies are present with subclinical disease because of sudden specific T cell clone activation.

The development of combination immunotherapies coupling an anti-PD-1 antibody with an anti-CTLA-4 antibody, could induce a greater prevalence of this immune side effect. A product characteristic study including the Bristol–Myers Squibb (BMS)067, BMS069 and CA209004-8 cohorts ($n = 448$ patients), based on combined immunotherapies, i.e. anti-PD-1 with anti-CTLA-4 antibodies, found one case of diabetes with ketoacidosis (0.223%). This observation is not very different from those reported for 1728 patients treated with nivolumab alone, where one case of diabetes and two cases of diabetes with ketoacidosis were described (0.173%). Additional investigation is needed to identify which patients are at increased risk of developing this toxicity under checkpoint inhibitor immunotherapy.

Concerning the management of anti-PD-1 therapy in the 24 cases reported in this literature review, treatment was temporarily discontinued in six (25%) patients [9–11, 13, 14, 17], as a result of symptom severity (until glycaemia was controlled) and resumed without effect on glycaemia, as in our patient's case. In three (12.5%) cases, anti-PD-1 therapy appears to have been continued alongside glycaemia control by insulin therapy [6, 12, 14, 18]. There was no information on this aspect for seven patients. All patients across the literature review remained under insulin therapy except for one Caucasian patient [5], whose treatment was permanently stopped due to progression of metastatic disease with subsequent decrease in glycaemia and insulin requirements, an increase in C-peptide levels and normalization of HbA1c. Insulin was gradually tapered down and then stopped, suggesting a reversible phenomenon. In one case, glucocorticoid treatment was started to reverse beta islet destruction, but was unsuccessful [15].

Conclusion

We describe a new case of autoimmune diabetes related to anti-PD-1 therapy with retrospective biological analyses, accompanied by a literature review enabling a characterization of autoimmune diabetes resulting from treatment toxicity. It also provided information on management of this rare but increasingly reported immune-related side effect. The potential severity of this complication, with frequent onset of fulminant diabetes, should motivate glycaemia monitoring during immunotherapy treatment. The question of whether autoantibodies should be screened for to identify high-risk subjects at treatment initiation needs to be evaluated.

Author Contributions Marie-Léa Gauci, Philippe Boudou, Céleste Lebbé and Jean-François Gautier had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to study conception, and subsequent acquisition, analysis and interpretation of data. All authors made substantial scientific and intellectual contributions to the drafting and rewriting of the initial and revised manuscript.

Funding sources This research did not receive any specific grant from any funding agencies in the public, commercial or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the participant in the study.

References

1. Robert C, Long GV, Brady B et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372:320–330. doi:10.1056/NEJMoa1412082
2. Wang J, Yoshida T, Nakaki F et al (2005) Establishment of NOD-Pdcd1−/− mice as an efficient animal model of type I diabetes. Proc Natl Acad Sci USA 102:11823–11828. doi:10.1073/pnas.0505497102
3. Rajasalu T, Brosi H, Schuster C et al (2010) Deficiency in B7–H1 (PD-L1)/PD-1 coinhibition triggers pancreatic β-cell destruction by insulin-specific, murine CD8 T-cells. Diabetes 59:1966–1973. doi:10.2337/db09-1135
4. Guleria I, Gubbels Bupp M, Dada S et al (2007) Mechanisms of PDL1-mediated regulation of autoimmune diabetes. Clin Immunol 125:16–25. doi:10.1016/j.clim.2007.05.013
5. Hansen E, Sahasrabudhe D, Sievert L (2016) A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. Cancer Immunol Immunother 65:765–767. doi:10.1007/s00262-016-1835-4
6. Martin-Liberal J, Furness AJS, Joshi K et al (2015) Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother 64:765–767. doi:10.1007/s00262-015-1689-1
7. Mellati M, Eaton KD, Brooks-Worrell BM et al (2015) Anti-PD-1 and anti-PDL-1 monoclonal antibodies causing type 1 diabetes. Diabetes Care 38:e137–e138. doi:10.2337/dc15-0889
8. Hughes J, Vudattu N, Sznol M et al (2015) Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 38:e55–e57. doi:10.2337/dc14-2349
9. Gaudy C, Clévy C, Monestier S et al (2015) Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. Diabetes Care 38:e182–e183. doi:10.2337/dc15-1331
10. Munakata W, Ohashi K, Yamauchi N, Tobinai K (2017) Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. Int J Hematol 105:383–386. doi:10.1007/s12185-016-2101-4
11. Teramoto Y, Nakamura Y, Asami Y et al (2017) Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. J Dermatol 44:605–606. doi:10.1111/1346-8138.13486
12. Miyoshi Y, Ogawa O, Oyama Y (2016) Nivolumab, an anti-programmed cell death-1 antibody, induces fulminant type 1 diabetes. Tohoku J Exp Med 239:155–158. doi:10.1620/tjem.239.155
13. Okamoto M, Okamoto M, Gotoh K et al (2016) Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. J Diabetes Investig 7:915–918. doi:10.1111/jdi.12531
14. Hofmann L, Forschner A, Loquai C et al (2016) Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 60:190–199. doi:10.1016/j.ejca.2016.02.025
15. Aleksova J, Lau PKH, Soldatos G, McArthur G (2016) Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma. BMJ Case Rep 2016:2016217454. doi:10.1136/bcr-2016-217454
16. Lowe JR, Perry DJ, Salama AKS et al (2016) Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy. J Immunother Cancer 4:89. doi:10.1186/s40425-016-0196-z
17. Usui Y, Udagawa H, Matsumoto S et al (2017) Association of serum anti-GAD antibody and HLA haplotypes with type 1 diabetes mellitus triggered by nivolumab in patients with non-small cell lung cancer. J Thorac Oncol 12:e41–e43. doi:10.1016/j.jtho.2016.12.015
18. Chae YK, Chiec L, Mohindra N et al (2017) A case of pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. Cancer Immunol Immunother 66:25–32. doi:10.1007/s00262-016-1913-7
19. Ishikawa K, Shono-Saito T, Yamate T et al (2017) A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. Eur J Dermatol 27:184–185. doi:10.1684/ejd.2016.2923
20. Imagawa A, Hanafusa T, Miyagawa JI et al (2000) A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. N Engl J Med 342:301–307. doi:10.1056/NEJM200002033420501
21. Moreau C, Drui D, Arnault-Ouary G et al (2008) Fulminant type 1 diabetes in Caucasians: a report of three cases. Diabetes Metab 34:529–532. doi:10.1016/j.diabet.2008.05.003
22. Imagawa A, Hanafusa T, Awata T et al (2012) Report of the committee of the Japan Diabetes Society on the research of fulminant and acute-onset type 1 diabetes mellitus: new diagnostic criteria of fulminant type 1 diabetes mellitus (2012). J Diabetes Investig 3:536–539. doi:10.1111/jdi.12024
23. Lampasona V, Liberati D (2016) Islet autoantibodies. Curr Diab Rep 16:53. doi:10.1007/s11892-016-0738-2
24. Kochupurakkal NM, Kruger AJ, Tripathi S et al (2014) Blockade of the programmed death-1 (PD1) pathway undermines potent genetic protection from type 1 diabetes. PLoS ONE 9:e89561. doi:10.1371/journal.pone.0089561
25. Fujisawa R, Haseda F, Tsutsumi C et al (2015) Low programmed cell death-1 (PD-1) expression in peripheral CD4(+) T cells in Japanese patients with autoimmune type 1 diabetes. Clin Exp Immunol 180:452–457. doi:10.1111/cei.12603