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ORIGINAL ARTICLE

Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: description of pancreatic endocrine and exocrine phenotype

Lucien Marchand[1] · Arnaud Thivolet[2] · Stéphane Dalle[3,4] · Karim Chikh[5] · Sophie Reffet[1] · Julien Vouillarmet[1] · Nicole Fabien[6] · Christine Cugnet-Anceau[1,4] · Charles Thivolet[1,7]

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Abstract

Aims Programmed cell death-1 and programmed death ligand 1 (PD-1/PD-L1) inhibitors restore antitumor immunity, but many autoimmune side-effects have been described. Diabetes mellitus is a rare complication, and little data concerning its pathophysiology and phenotype have been published. This study aimed to describe both pancreatic endocrine and exocrine functions, immunological features and change in pancreas volume in subjects with diabetes mellitus induced by PD-1 and PD-L1 inhibitors.

Methods We analyzed the data of six subjects treated with immunotherapy who presented acute diabetes.

Results There were five men and one woman. Median age was 67 years (range 55–83). Three subjects were treated with nivolumab, two with pembrolizumab and one with durvalumab. Median time to diabetes onset after immunotherapy initiation was 4 months (range 2–13). Four patients presented fulminant diabetes (FD); none of these had type 1 diabetes (T1D)-related autoantibodies, none of them had T1D or FD-very high-risk HLA class II profiles. The bi-hormonal endocrine and exocrine pancreatic failure previously reported for one FD patient was not found in other FD subjects, but glucagon response was blunted in another FD patient. Pancreas volume was decreased at diabetes onset in 2 FD patients, and all patients presented a subsequent decrease of pancreas volume during follow-up.

Conclusions In the patients presented herein, immunotherapy-induced diabetes was not associated with T1D-related autoantibodies. The hormonal and morphological analysis of the pancreatic glands of these six cases contributes to the understanding of the underlying and probably heterogeneous mechanisms. There is a need to find biomarkers to identify patients at risk to develop these new forms of diabetes at early stages of the process to prevent ketoacidosis and to evaluate preventive strategies.

Keywords Diabetes mellitus · Fulminant diabetes · Autoimmune diabetes · Immune checkpoint inhibitors side-effects · Immunotherapy · Programmed cell death-1 · Anti-PD-1 · Programmed death ligand 1 · Anti-PD-L1 · Pancreas volume · Beta-cell pancreatic function · Alpha-cell pancreatic function · Exocrine pancreatic function · Mixed meal test

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✉ Lucien Marchand
lucien.marchand@chu-lyon.fr

[1] Department of Endocrinology and Diabetes, Hospices Civils de Lyon, Lyon-Sud Hospital, 165 chemin du Grand Revoyet, Pierre-Bénite 69310, France

[2] Department of Radiology, Hospices Civils de Lyon, Lyon, France

[3] Department of Dermatology, Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre-Bénite, France

[4] ImmuCare (Immunology Cancer Research), Hospices Civils de Lyon, Lyon, France

[5] Department of Biochemistry, Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre-Bénite, France

[6] Department of Immunology, Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre-Bénite, France

[7] CarMeN Laboratory (INSERM U1060, INRA U1235, Université Claude Bernard Lyon1, INSA-Lyon), Lyon 1 University, Oullins, France

Introduction

Immune checkpoint inhibitors are being increasingly used to treat solid tumors. They include cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors (ipilimumab and tremelimumab), programmed death 1 (PD-1) inhibitors (nivolumab and pembrolizumab), and programmed death ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab and durvalumab). Blocking either PD-1 or PD-L1 promotes activation of cytotoxic T cells, triggers an immune-mediated anti-tumor response [1] but has been associated with many immune-related toxicities [2]. Several endocrine side-effects have been reported, mainly hypophysitis (more frequent with anti-CLTA-4 agents) or thyroid dysfunction (more frequent with anti-PD-1/PD-L1 agents). Furthermore, it has been shown that PD-1 and PD-L1 inhibitors precipitate diabetes in an animal model (prediabetic non-obese diabetic (NOD) mice) [3]. Stamatouli et al. described recently the largest case series of insulin-dependent diabetes induced by anti-PD-1 or anti-PD-L1 antibodies (27 cases) and reported that the prevalence was 0.9% [4]. More than half of the cases were similar to fulminant diabetes (FD), a type of diabetes initially described in East-Asian populations (mostly Japanese patients), with extremely acute onset and a near-normal HbA1c [5], that is usually exceptional in Caucasian subjects [6].

We previously reported the case of a 55-year-old Caucasian man with advanced pulmonary pleomorphic carcinoma treated with nivolumab who had, in parallel to a prolonged tumor response [7], FD with bi-hormonal pancreatic failure, decrease of exocrine pancreatic function, and acute pancreas atrophy [8]. In the reported cases of Japanese FD and anti-PD1/PD-L1-induced FD, alpha-cell and exocrine functions were not detailed or explored, so it remains to be determined whether these features are usual or not in FD. In this context, we have carefully explored both endocrine and exocrine pancreatic functions of six subjects who presented anti-PD1/PD-L1-induced diabetes, including four who presented an FD.

Methods

A total of six Caucasian patients treated with immune checkpoint inhibitors who presented diabetes mellitus until February 2018 and referred to our center were included. The reported investigations were carried out in accordance with the principles of the declaration of Helsinki as revised in 2008 and subjects were included in the analysis after informed consent.

FD was defined by a very acute onset with ketoacidosis, an HbA1c ≤ 8.5% and undetectable C-peptide [9]. Sera taken at diabetes onset were tested for type 1 diabetes (T1D)-related autoantibodies, i.e., anti-glutamic acid decarboxylase (GAD), anti-insulinoma antigen-2 (IA-2), and anti-zinc transporter 8 autoantibodies (ZnT8), using an enzyme-linked immune-sorbent assay (ELISA; Medizym®, Medipan, GMBH, Dahlewitz, Germany) according to manufacturer's instructions. Human leukocyte antigen (HLA) class I and II were analyzed using specific polymerase chain reaction sequence-specific oligonucleotides (Luminex, One Lambda, Kittridge, USA).

C-peptide was measured using a conventional assay (Cobas e411; Roche Diagnostics, Switzerland); C-peptide was also tested using an ultrasensitive assay for subjects with FD (ELISA; Mercodia, Uppsala Sweden) both at basal state and after a mixed meal test (MMT) with a standard preparation of fat, carbohydrate, and protein (Delical HP-HC, Lactalis, Torcé, France) at a dose of 4 ml/kg (6 kcal/kg) and a maximum volume of 360 ml. To further explore alpha-cell function, subjects with FD underwent a 2-h MMT 1 month after diabetes onset. Glucagon was measured by a solid-phase two-site enzyme immunoassay (Mercodia). The glucagon response was compared to 15 C-peptide–negative (ultrasensitive assay) patients with long-standing type 1 diabetes (median age 33 years, range 25–48; median duration of diabetes 14 years, range 4–19).

The exocrine pancreatic function was explored through fecal elastase-1 (ELISA; ScheBo® Biotech AG, Giessen, Germany). Exocrine pancreas antibodies (EPA) were measured using an indirect immunofluorescence assay using monkey pancreas as substrate (InGen, Chilly, France). IgG and IgA isotype anti-exocrine-pancreatic glycoprotein 2 (one of the major antigens of exocrine pancreas) antibodies (GP2A) were measured using ELISA (Generic Assays, Dahlewitz, Germany), and indirect immunofluorescence test (IIFT) techniques (Labodia, Medipan).

Pancreas volume was assessed by a radiologist on manual segmentations and 3D rendering reconstructions from portal venous phase contrast-enhanced CT images and a post-processing software (IntelliSpace Portal 9.0, Philips Healthcare) using an interactive contour delineation tool (Smart Brush). Evolution of pancreas volume was also studied in a control group of 4 patients treated with a PD-1 inhibitor (nivolumab or pembrolizumab) in a context of melanoma, who did not present diabetes during treatment, matched for age and sex [4 men, with median age of 70 years (range 56–76)]. A 18F-FDG PET/CT was performed 6 days before diabetes in subject #6 to monitor muscle metastasis.

Statistical analysis was performed with GraphPad prism 7.04 software using unpaired t test or one-way analysis of variance (ANOVA) when appropriate. A p value < 0.05 was considered significant.

Results

Baseline characteristics of the six patients are detailed in Table 1. There were five men and one woman, and the median age was 67 years (range 55–83). Three subjects had a metastatic melanoma, one a pulmonary adenocarcinoma, one a pleiomorphic pulmonary carcinoma, and one a cutaneous T-cell lymphoma. Three subjects were treated with nivolumab, two with pembrolizumab, and one with durvalumab. Subject #6 was also treated by anti-CTLA4 antibody (ipilimumab; intratumoral injection). None had systemic glucocorticoids. The median time to diabetes onset after initiation of immunotherapy was 4 months (range 2–13), and median number of anti-PD-1/PD-L1 courses was 7 (range 3–13). Three subjects presented an additional endocrine side-effect (2 with Hashimoto's disease, 1 with corticotroph insufficiency). Four subjects presented a partial tumor response according to RECIST criteria. Anti-PD-1/PD-L1 treatment was resumed in two subjects once diabetes was controlled with subcutaneous insulin.

The clinical and biochemical data at diabetes onset are detailed in Table 2. None of the subjects had a familial

Table 1 Baseline characteristics

Patient #	1	2	3	4	5	6
Age (years)	55	72	69	83	65	65
Gender	M	M	M	M	M	W
Previous medical history	No	Hypertension, dyslipidemia	Melanoma, deep vein thrombosis	Hypertension, right nephrectomy	No	No
Neoplasia	Pulmonary pleomorphic carcinoma	Cutaneous T-cell lymphoma	Pulmonary adenocarcinoma	Melanoma	Melanoma	Melanoma
Sites of metastases	Adrenal glands	NA	No	Lymph nodes	Skin and parotid	Liver, bones, muscles, pancreas, cerebellum
Anti-PD-1/PD-L1	Nivolumab	Nivolumab	Durvalumab	Pembrolizumab	Pembrolizumab	Nivolumab
Associated immunotherapy	No	No	No	No	No	Ipilimumab (intratumoral injection)
Prior chemotherapy	Docetaxel and cisplatin	Methotrexate, bexarotene, gemcitabine, vorinostat, mogamulizumab	Vinorelbine and cisplatin	No	No	No
Associated chemotherapy	No	Brentuximab vedotin	No	No	No	No
Associated glucocorticoids	No	No	No	No	No	No
Frequency of anti-PD-1/PD-L1 courses (weeks)	2	2	4	3	3	3
Number of courses before diabetes onset	9	3	13	4	12	5
Time to diabetes onset (months)	5	2	13	2.5	8.5	3
Other side-effects	Corticotroph insufficiency	Diarrhea, alopecia	Asthenia, maculopapular rash with pruritus	Hashimoto's disease, maculopapular rash	Hashimoto's disease	Hypereosinophilia
Partial response (RECIST)	Yes	Yes	NA	Yes	No	Yes
Toxicity (grade)	4	3	4	3	4	4
Definitive discontinuation of anti-PD-1/PD-L1	No	Yes	Yes	No	Yes	Yes

Table 2 Clinical and biochemical data at diabetes onset

Patients	1	2	3	4	5	6
Familial history of diabetes	No	No	No	No	No	No
BMI at onset (kg/m^2)	20.9	26	23.2	26	24	21.7
Presentation	Fulminant diabetes	Polyuria–polydipsia syndrome	Fulminant diabetes	No symptoms	Fulminant diabetes	Fulminant diabetes
Glycemia (mmol/l)	27.7	25	31	33	32	44
Ketoacidosis	Yes	No	Yes	No	Yes	Yes
% weight loss at onset	6.5	9.6	4.7	None	6.2	5.0
HbA1c as % (mmol/mol)	8.2 (66)	11.4 (101)	7.4 (57)	9.4 (79)	8.5 (69)	7.3 (56)
C-peptide nmol/l, ($N > 0.37$)	< 0.1	1	< 0.1	1	< 0.1	< 0.1
GADA UI/ml ($N < 5$)	< 1	1	< 1	1	< 1	1.3
IA-2A UI/mL ($N < 10$)	0.4	22.8	< 1	2.8	0.2	0.2
ZnT8A U/mL ($N < 15$)	0.6	1.3	< 1	0.3	0.7	0.8
HLA	DRB1*12:01 DQA1*01 DQB1*03:01/ DRB1*15:01 DQA1*05 DQB1*06:02	DRB1*04:01 DQA1*01 DQB1*03:01/ DRB1*13:02 DQA1*03 DQB1*06:04	DRB1*04:05 DQA1*02 DQB1*02:02/ DRB1*07:01 DQA1*05 DQB1*03:02	DRB1*01:01 DQA1*01 DQB1*05:01/ DRB1*16:01 DQA1*01 DQB1*05:02	DRB1*04:01 DQA1*02 DQB1*02:02/ DRB1*07:01 DQA1*03 DQB1*03:01	DRB1*01:01 DQA1*01 DQB1*03:01/ DRB1*11:01 DQA1*05 DQB1*05:01
Lipasemia UI/L ($N < 78$)	NA	88	NA	19	178	562
Fecal elastase-1 ug/g ($N > 200$)	110	NA	215	143	500	370
EPA (N < 10)	< 10	< 10	< 10	< 10	< 10	< 10
IgA GP2A	Negative	Negative	Positive	Negative	Negative	Negative
Ferritinemia ug/L ($N < 300$)	2048	NA	215	143	1055	425
HDL-c (mmol/l)	0.46	NA	1.47	1.06	1.17	1.68
LDL-c (mmol/l)	3.77	NA	4.58	2.84	3.03	3.87
Triglycerides (mmol/l)	2.62	NA	1.36	0.97	1.40	1.72
TSH (mUI/l)	1.7	2.3	1.14	2.62	30	2.43
TPOA UI/ml ($n < 30$)	1	10	15	277	37	8

BMI body mass index, *GADA* glutamic acid decarboxylase autoantibodies, *IA–2A* anti-insulinoma antigen-2 autoantibodies, *ZnT8A* zinc transporter 8 autoantibodies, *EPA* exocrine pancreas antibodies, *GP2A* exocrine-pancreatic glycoprotein 2 antibodies, *TPOA* thyroid peroxidase antibodies, *NA* data not available

history of diabetes. Median body mass index (BMI) was 23.6 kg/m^2 (range 20.9–26). Four subjects presented FD; in the 2 other subjects C-peptide was still detectable. Those with FD were negative for T1D-related autoantibodies, but subject #2 was positive for IA-2A. C-peptide (ultrasensitive assay) was undetectable before and after MMT 1 month after diabetes onset in subjects with FD. As compared to subjects with classical T1D, glucagon response was blunted for subjects #1 and #6 (Fig. 1). There was no significant difference between the mean (± standard error of the mean, SEM) values of FD subjects (8.26 ± 1.04 pmol/l) and those with T1D (11.06 ± 1.13 pmol/l, $p = 0.09$), but a significant difference was found in one-way ANOVA ($p = 0.0001$, R square 0.526). AUC of glucagon responses were lower in subjects #1 and #6 (respectively, 31.15 and 33.02 pmol/l) than subjects #3 and #5 (respectively, 73.2 and 72.38 pmol/l) and patients with T1D (mean 69.13 pmol/l). Glucose responses during MMT are presented in Supplemental Table 1.

None of the subjects had a sign of acute or chronic pancreatitis on CT scans or report abdominal pain. Three patients had an increased lipasemia at diabetes onset; this was clinically significant in 2 subjects with FD (#5 and 6) and was subnormal in subject #2. Fecal elastase-1 was decreased in 2 subjects (patients #1 (FD) and #4). All 6 patients were negative for antibodies against exocrine pancreas using IFI, but one out of 6 subjects (patient # 3 (FD)) was positive for IgA GP2A.

Analysis of pancreas volume showed a slight increase in 3 FD subjects before diabetes onset (subjects #1, #3, and #6). Pancreas volume decreased at diabetes onset for 2 subjects with FD (subjects #1 and #5), but there was no reduction in pancreatic volume at onset of diabetes for the 2 subjects with diabetes without ketoacidosis (subjects #2 and #4). There was a subsequent atrophy in all the subjects (Fig. 2 and Supplemental Fig. 1). The last available pancreatic volumes were significantly reduced in patients with FD compared to the others (mean ± SEM 40.8 ± 5.46 vs 88 ± 11 cm^3, $p < 0.01$). In contrast, control patients who did not experience diabetes after immunotherapy had comparable pancreatic volume between initial analysis and after a median period of 12.5 months of treatment (range 6–36) (Supplemental Table 2).

The four subjects with FD as well as subject #4 remained insulin-dependent at last follow-up (range 8–24 months), whereas subject #2 discontinued insulin 3 months after diabetes onset and was still free from anti-diabetic drug 1 year after anti-PD-1/PD-L1 treatment withdrawal.

Discussion

We report herein a series of immunotherapy-induced diabetes mellitus, with a detailed description of diabetes phenotype and with an analysis of pancreas volume.

In published case series and literature reviews [4, 10], approximately 50% of subjects presented at least one T1D-related autoantibody. In the present case series, only 1 subject was positive for a T1D-related autoantibody (IA-2A),

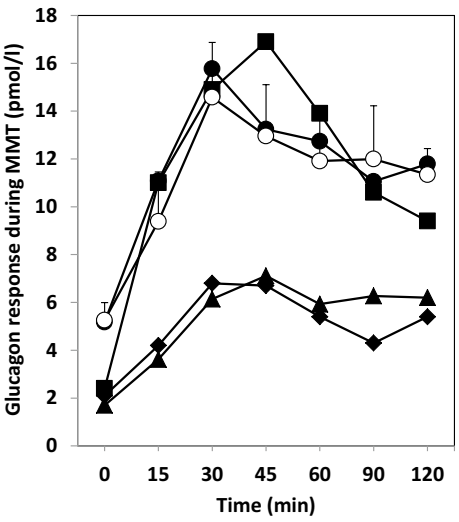

Fig. 1 Glucagon response during mixed meal test. The glucagon response of the four subjects with fulminant diabetes (black symbols) was compared to the mean ± SEM response of 15 C-peptide–negative (ultrasensitive assay) patients with classical T1 diabetes (open circles). Subject #1 (diamond), subject #3 (square), subject #5 (circle), subject #6 (triangle)

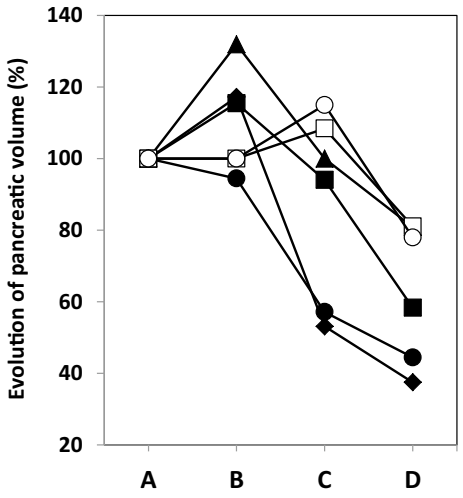

Fig. 2 Change in pancreas volume during immunotherapy. The pancreas volume was measured on CT-scan before immunotherapy initiation (A), on the last CT-scan available before diabetes onset (B), at diabetes onset (C), and on the last CT-scan available after diabetes onset (D) in patients with fulminant diabetes (closed symbols) or in subjects with detectable C-peptide (open symbols). Subject #1 (diamond), subject #2 (square), subject #3 (square), subject #4 (circle), subject #5 (circle), subject #6 (triangle)

but surprisingly this corresponded to a transient form of diabetes and all 4 patients with FD were GADA, IA-2, and ZnT8A negative. This highlights the sharp contrast in the immunological features in such cases to that known for classical autoimmune T1D with the same analytical methods [11].

Rui et al. [12] have reported that PD-L1 is expressed on the beta-cells of NOD mice. PD-1 and PD-L1 inhibitors are effective in oncology because they activate tumor-reactive T cells. We can speculate that blockade of PD-1 or PD-L1 can cause FD after a sudden and major activation of beta cell-reactive CD8 + T cell clones, without the participation of humoral immunity in the short time frame before clinical diabetes. This is supported by the completely abolished C-peptide response to MMT performed 1 month after diagnosis despite the use of an ultrasensitive assay, in contrast to what is generally observed during the first year of classical T1D [13]. It therefore seems that there are no beta-cells left in such patients and rescue therapy with glucocorticoids or other immune interventions initiated after ketoacidosis would be futile.

It is of note that none of the subjects reported herein presented the class II haplotypes of FD described in a Japanese population (DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03) [9]. None of them were homozygous for T1D very high-risk HLA Class II haplotypes (DRB1*04:01-DQB1*03:02 or DRB1*03-DQB1*02) or heterozygous with the 2 haplotypes [14, 15]. Interestingly, subjects #1 and #6 (FD) and subject #2 displayed HLA class II haplotypes that usually confer protection against T1D (respectively, DRB1*15:01-DQB1*06:02, DRB1*11:01-DQB1*03:01 and DRB1*13-DQB1*06).

Two subjects with FD (#5 and #6) had an increased level of lipase during diabetes onset without abdominal pain, malabsorption symptoms, or sign of acute pancreatitis on analysis of CT scans (lipasemia was not investigated in the 2 other FD subjects). The increase in pancreatic exocrine enzymes has been described in classical Japanese FD [5], but also in patients treated by PD-1/PD-L1 agents that do not have diabetes [16] (pancreatitis is a rare side effect of PD-1/PD-L1 [2]). In the series reported by Stamatouli et al. [4], 42% of subjects had evidence of pancreatitis in the peridiagnosis period of diabetes (elevated lipase level and/or pancreatic edema), but no clinical information about the presence or absence of abdominal pain for the subjects, or regarding subsequent clinical symptoms of exocrine deficiency, such as steatorrhea, was reported limiting interpretation. Furthermore, random glucagon levels (tested only in four subjects) were not reduced, and the authors suggested that alpha-cells were not affected [4]. Interestingly, in the series presented herein exocrine pancreatic insufficiency was present in two subjects (#1 (FD) and #4) and subjects #1 and #6 (both FD) had a blunt glucagon response during MMT in comparison to C-peptide-negative T1D patients. Exaggerated plasma glucagon responses to MMT are observed in subjects with T1D within the first 2 years of diagnosis in comparison to non-diabetic subjects [17], and in this present series it would have been helpful to compare glucagon responses of these four FD subjects with non-diabetic subjects. Subject #6 had an initial pancreatic metastasis of a melanoma that disappears after 2 months of nivolumab suggesting a local and effective activation of cellular immunity. A 18F-FDG PET/CT was performed 6 days before diabetes onset, but did not show pancreas hypermetabolism. In case of an acute or autoimmune pancreatitis, an increase of pancreas uptake would have been expected [18]. It can be concluded from these observations, that the diabetes phenotype of subject #1 appears to be unusual and that the hypothesis of an associated pancreatitis does not apply to all cases with FD. In our opinion, there is a need to explore carefully pancreatic endocrine alpha-cell function with MMT and exocrine function in these patients to conclude whether the autoimmune destruction is specific of islet beta-cells or not.

Immunological analysis of EPA in subjects with immunotherapy-induced diabetes has not been done previously. Some studies found that subjects with T1D could have antibodies against exocrine pancreatic enzymes/cells antigens [19, 20]. Herein, all subjects were negative for EPA, only one FD subject was positive for GP2A, but further analyses of pancreatic autoantibodies in larger populations are required.

Some previous studies have demonstrated that pancreatic volume is decreased in T1D [21–23], but these analyses were rarely really performed at onset of diabetes. Herein, the analysis of pancreas volume found that there was a decrease in two subjects with FD at diabetes onset, which was not found in the two patients with preserved C-peptide. This observation could reinforce the previous idea of a paracrine insulinotropic effect on exocrine tissue [24], but we noted a subsequent decrease in pancreas volume in all subjects (including subject #2 who discontinued insulin 3 months after diabetes onset) which suggests more complex interpretations. Reduction of pancreatic volume was specifically associated with diabetes and not with immunotherapy. An increase in pancreas volume was noted for three subjects with FD several weeks before acute onset of diabetes. However, to prove that the pancreatic gland of these patients displays inflammation, only histological analysis would provide definite conclusions.

The relationship between exocrine and endocrine tissues in autoimmune diabetes remains largely unexplored, despite some observations [25–28], and a better knowledge of this relationship would be extremely useful to further the understanding of immunotherapy-induced diabetes as well as the classical form of autoimmune T1D.

The diabetes profile of subjects #2 and #4 were different from those with FD: they had a higher BMI (both 26 kg/m^2) than subjects with FD (range 20.9–24), were older (72 and 83 years, vs. 55–69 years for FD subjects), and had previous history of hypertension. The metabolic context for these 2 patients seemed therefore to be different from those with FD. A recent study concluded that there was a trend for glycemia increase with anti-PD1 infusions in subjects with preexisting type 2 diabetes (but overall in the total population there was no general tendency to glycemic disorders) [29].

In conclusion, these new forms of drug-induced diabetes differ from classical T1D. With the hormonal and morphological analysis of the pancreatic glands of the 6 cases, we contribute to the understanding of the underlying and probably heterogeneous mechanisms. As anti-PD-1 and anti-PD-L1 agents are increasingly used in oncology, there is a need to find biomarkers to identify the patients at risk to develop these new forms of diabetes at early stages of the process to evaluate rescue strategies and to prevent ketoacidosis.

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Author contributions LM and CT collected clinical data and wrote the manuscript. LM, SR, JV, CCA and CT were clinicians in charge of managing patients' endocrinopathies. AT analyzed the evolution of pancreas volume. NF tested autoantibodies. KC tested glucagon and C-peptide levels. SD analyzed the data, reviewed/edited the manuscript and contributed to the discussion. All authors gave final approval of the version to be published. CT is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that there is no duality of interest associated with this manuscript.

Research involving human participants and/or animals All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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