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Long-Term Persistent Absolute Insulin Secretion Deficiency in Diabetes Induced by Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors are today an immense hope in the management of cancers. However, since their widespread use, many cases of insulin-requiring diabetes appearing suddenly, as fulminant diabetes have been reported. Here, we describe 4 cases that occurred at different times after the beginning of immune checkpoint inhibitor therapy with Nivolumab alone or associated with Ipilimumab. There are 3 cases of newly diagnosed diabetes and 1 case of known type 2 diabetes formerly quite well balanced with Metformin. The clinical and biological characteristics of these patients are quite similar. They were all insulin-requiring at the discovery of diabetes and remained so throughout their follow-up. This type of diabetes which looks like type 1 diabetes seems rather to be a new entity.

Keywords

Immune Checkpoint Inhibitors, Nivolumab, Ipilimumab, Fulminant Diabetes, Insulin-Requiring Diabetes

1. Introduction

Immunotherapy has revolutionized the management of cancer and has offered great hope for patients with metastases. It's a therapeutic approach that acts on the immune system involved in the recognition and destruction of tumors by inhibiting immune checkpoints which are actually physiological mechanisms of inactivation of the immune system after its activation.

Indeed, to achieve a cellular immune response, antigens from primary mela-

noma are presented to naive lymphocytes expressing TCR (T Cell Receptor) and CD28 (Cluster of Differentiation 28) by antigen-presenting cells expressing MHC (Major Histocompatibility Complex) and the B7 complex. Thus, the interaction of TCR and CD28 with the MHC and the B7 complex respectively, induces an activation of the T lymphocyte which produces cytokines and acquires antigenic memory. CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4) appears on the surface of the activated lymphocyte 24 to 48 hours after the initial presentation of the antigen and, by binding to the B7 complex, results in lymphocyte deactivation. The activated T lymphocyte expresses on its surface the PD-1 (Programmed Death 1) receptor which, by binding to its PDL-1 or 2 ligand (Programmed Death Ligand 1/2) expressed on the surface of tumor cells, inhibits its cytotoxic activity. Nivolumab, an anti-PD-1 antibody and Ipilimumab, an anti-CTLA4 antibody, by inhibiting these immune checkpoints, activate the immune system in a non-specific and diffuse manner and thus induce an anti-tumor effect. [1]. This therapeutic revolution is unfortunately associated with numerous side effects.

Thereby, many autoimmune diseases particularly those concerning endocrine glands have been reported with immune checkpoint inhibitors [2] [3]. Several authors have reported numerous cases of insulin-dependent diabetes induced by immune checkpoint inhibitors in recent years [4] [5] [6] [7]. We already have reported our first case of insulin-dependent diabetes induced by immune checkpoint inhibitors [8]. Much is unknown about the duration of this insulin dependence.

We report 4 cases of insulin-dependent diabetes diagnosed during immune checkpoint inhibitors therapy for melanoma and who have remained insulin-dependent after several years of follow-up.

All participants had known to participate in the study and had given their consent (Table 1).

Table 1. Characteristic of patients at diagnosis.

	Case 1	Case 2	Case 3	Case 4
Age at discovery	24	65*	37	73
Mode of revelation	Ketoacidosis	Ketoacidosis	Without ketosis	Ketoacidosis
HbA1c (%)	5.9	9.3	5.4	8.8
Anti-langherans beta cell antibodies	Negative	Negative	Negative	Positive: anti GAD anti ZnT8 anti IA2
C Peptide	Undetectable	Undetectable	Undetectable	Undetectable
BMI (kg/m²)	18.9	24.5	20.3	31.1
Immune checkpoint inhibitor used at the diagnostic	Nivolumab and Ipilimumab	Nivolumab and Ipilimumab	Nivolumab	Nivolumab
Duration of treatment (week)	4	4	33	6
Number of cure	2	2	17	3

2. Case 1

It's a 24-year-old patient, with no personal or family history of diabetes, followed for melanoma. She was included in a therapeutic protocol combining Ipilimumab and Nivolumab. After 4 weeks and on the eve of the 3rd chemotherapy dose, she was admitted to the emergency department for the discovery of diabetic ketoacidosis without coma. The Interrogation finds a sudden onset of polyuria and polydipsia followed by nausea and vomiting. Biological examinations have shown blood sugar at 22 mmol/l, ketonemia at 3.8 mmol/l and bicarbonates at 15 mmol/l. The blood sugar obtained 2 weeks earlier was normal at 4.55 mmol/l. Glycated hemoglobin (HbA1c) was 5.9%, C-peptide was undetectable as well as anti-ZnT8 (Zin Transporteur 8), anti-GAD (Glutamic Acid Decarboxilase) and anti IA2 (Tyrosine Phosphatase). She had a normal weight (BMI [Body Mass Index] at 18.9 kg/m^2). Optimal glycemic control has been achieved with insulin therapy. After more than 3 years of follow-up, insulin was still required to achieve the blood glucose target (A1c level = 7.6%), and C-peptide and type 1 diabetes-associated antibodies were still undetectable.

3. Case 2

It's a 65-year-old patient who has been known to have type 2 diabetes since 23 years ago and has normal weight (BMI = 24.5 kg/m^2). The diabetes was relatively well controlled by Metformin with an HbA1c of 7.9%. He is followed for melanoma of the left hallux initially treated with Pembrolizumab (7 cures). After a dissociated response he has benefited from Nivolumab associated with Ipilimumab. Four weeks after the beginning of this new therapeutic line and four days after the administration of the 2nd cure, the patient was admitted to the emergency department for diffuse myalgia, vomiting and polypnea. The diagnosis of diabetic ketoacidosis was made with a pH of 6.9 and bicarbonates at 2 mmol/l. This ketoacidosis was the first episode in this patient. Anti-ZnT8, anti-GAD and anti IA2 antibodies were negative, HbA1c was at 9.3% and C- peptide was undetectable. Insulin therapy helped to achieve good glycaemic control. After three months of follow-up, the patient remained insulin-requiring.

4. Case 3

He is a 37-year-old patient with no personal or family history of diabetes, followed for metastatic melanoma. After failure of a first-line treatment with Ipilumumab and a 2nd line with Nivolumab both as monotherapy, a combination of Ipilumumab and Nivolumab is initiated. After 4 cures of this combination, maintenance treatment with Nivolumab as monotherapy is set up because of a dissociated response. After 33 weeks of this maintenance treatment and 17 cures later, diabetes was discovered in the context of rapidly onset polyuria and polydipsia. A blood check showed a blood sugar at 4 g/l without ketosis and an HbA1c at 5.4%. The weight was normal (BMI at 20.3 kg/m^2). The anti-GAD, anti-ZnT8, anti-insulin and anti-IA2 antibodies were negative. The C peptide was

undetectable. Insulin allows us to achieve the glycemic goals. After more than 3 years of follow-up, the patient has remained insulin-requiring.

5. Case 4

Seventy-three-year-old patient, obese (BMI = 31.1 kg/m^2), with no history of diabetes, followed for melanoma. A 2nd therapeutic line with Nivolumab was initiated after the failure of a 1st line combining Vemurafenib and Combimetinib. Three cures and 6 weeks after the beginning of this new therapeutic line, diabetic ketoacidosis was diagnosed. The anti-GAD, anti-ZnT8, and anti-IA2 antibodies were all positive; the C peptide was undetectable and the HbA1c was at 8.8%, one month after the diabetes discovery. Retrospectively, from blood samples taken and stored before the start of treatment with Nivolumab, laboratory investigation already showed the presence of autoantibodies, but normal insulin, C-peptide secretion and glycaemia. Satisfactory glycaemic control is achieved with insulin therapy. After more than 3 years of follow-up, the C-peptide remains undetectable, and the patient has remained insulin-requiring.

6. Comments

Fulminant diabetes is a subtype of type 1 diabetes characterized by a sudden onset of high plasma glucose and ketoacidosis contrasting with near-normal glycated hemoglobin, absence of type 1 diabetes-related antibodies, and collapsed C-peptide. Underlying pathophysiological mechanisms remain unknown but viral pancreatitis has been suggested. It was first described in Japan more than twenty years ago, and after other cases were reported in other Asian countries [9] [10]. Although rarely described in the Caucasian population until now, it's increasingly common since the widespread use of immune checkpoint inhibitors [11]. Diabetes in our patients looks like this type of diabetes.

Table 1 summarizes the main characteristics of our patients at diagnosis. Thus, at the diagnosis of diabetes, half of the patients were treated with nivolumab associated with ipilimumab and the other half were treated with nivolumab as monotherapy. The number of cures (from 2 to 17) and the time from treatment onset to diabetes discovery (from 4 to 33 weeks) were variable. Only one patient had known type 2 diabetes who was well controlled under metformin before starting chemotherapy. Ketoacidosis was the mode of revelation of diabetes in 2 patients and the mode of decompensation of diabetes in the patient known as diabetic. HbA1c at onset was < 6% in 2 patients, 7.9% in the known diabetic and 8.8% in the oldest patient of the series who is also the only one to have anti-Langerhans bêta-cell antibodies. C-peptide was undetectable in all patients. The 3 patients have remained insulin-dependent after more than 3 years of follow-up. The type 2 diabetic patient known before the beginning of immune checkpoint inhibitors has also remained insulin-requiring during the 3 months of follow-up.

Cases of diabetes diagnosed during treatment with immune checkpoint inhi-

bitors are reported in the literature.

Stamatouli and al [12] have reported 27 cases of insulin-dependent diabetes that occurred during immune checkpoint inhibitory therapy for cancer. Two patients were known to have diabetes and were well-balanced on biguanide before the start of therapy. Ketoacidosis was the mode of discovery of diabetes in 59% of patients. Just over half of the patients were treated as monotherapy (nivolumab or pembrolizumab) and nivolumab associated with ipilimumab was the most association used. The median onset of diabetes was 20 weeks after the beginning of therapy. The C peptide was undetectable in 85% of patients. At least one anti-Langherans beta cell antibody was positive in 40% of patients. The mean HbA1c was 7.95% (6% - 10.5%).

Kapke and al [13] described 2 cases that had no history of diabetes. Ketoacidosis was the mode of revelation in the 2 patients. Diabetes was diagnosed 3 months after starting treatment with nivolumab in one patient and 2 months after starting treatment with atezolizumab in the other patient. They both had positive anti GAD antibodies and collapsed C peptides. These 2 patients remained insulin-dependent.

Tsang and al [14] collected 10 cases of which only one was known as diabetic and well-balanced under biguanide and sodium glucose transporter 2 inhibitor. In 4 patients, the mode of revelation of diabetes was ketoacidosis. At diagnosis of diabetes, 6 patients were treated with pembrolizumab, 3 patients with the combination nivolumab and ipilimumab and 1 patient with the combination pembrolizumab and ipilimumab after a median duration of 25 weeks [17.5 - 34.5]. The C peptide was collapsed or undetectable in 6 patients and only 2 patients had positive anti GAD antibodies. The median HbA1c was 7.6% [7.15 - 9.75]. All patients remained insulin-dependent for the duration of the follow-up (1 - 35 months).

7. Conclusion

Diabetes induced by immune checkpoint inhibitors is more and more frequent since their generalization in the treatment of cancers. It sometimes has some clinical and biological similarities with type 1 diabetes without being able to classify it as such even if the patients remain insulin dependent. Further studies will be necessary to better understand this type of diabetes, which seems to be a new entity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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