

Severe Ketoacidosis as the First Clinical Manifestation of Type 1 Diabetes Mellitus Secondary to Immune Checkpoint Inhibitors

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Abstract

Introduction Immunotherapy represents one of the fundamental points on the oncological treatments. The increasingly frequent use of these treatments has allowed us to observe various side effects in up to 10 to 20% of patients and endocrine side effects are one of the most commonly described. We report a case of diabetic ketoacidosis in a 46-year-old male patient as debut of type-1 diabetes mellitus secondary to treatment with nivolumab.

Case Report The patient who went to the emergency department due to abdominal pain associated with vomiting 48 hours previously. Diagnosed 4 years ago of clear cell renal carcinoma stage IV, due to pulmonary metastatic involvement, the patient was under treatment with nivolumab. Urgent blood and urine tests were performed in the urgency evaluation; the patient was diagnosis of severe diabetic ketoacidosis. Pancreatic endocrine complications are observed in 0.5 to 5% of the patients with immunotherapy. Among the adverse effects described are alterations in baseline fasting glycaemia and the possible development of type-1 diabetes. These molecules increase the activity of T-cells, amplify the cellular immune activity with the consequent increased immune response, which can lead to a destruction of the pancreatic β -cells. Strict endocrine control is necessary during immunotherapy treatment; however, there are no clear indications for the monitoring of pancreatic reserve levels or glycemic control. For these reasons, we propose the need for closer and regular monitoring of C-peptide and HbA1c (glycosylated hemoglobin) to prevent the development of the diabetes and their complications.

Keywords

- ▶ C-peptide
- ▶ immunotherapy
- ▶ ketoacidosis

Introduction

Oncological treatments are often based on immunotherapy. Immune control points (or “checkpoints”) include cell surface molecules that act as endogenous regulators of the immune response and, therefore, are perfect therapeutic targets.¹ One of the best-known checkpoints is the programmed cell death

protein 1 receptor (PD-L1 or programmed death 1) that is found on the surface of immune cells.^{2,3} When PD-L1 binds to its ligand (PD-L1 and PD-L2), the activation pathways of the immune cell are inhibited. Using various monoclonal antibodies, activation of the immune system can take place, acting at the receptor or ligand level, thereby enhancing anti-tumor activity.⁴

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The increasingly frequent use of these treatments has allowed us to observe various side effects, which occur in up to 10 to 20% of patients.^{5,6} Endocrine side effects are the most common type described for these drugs⁷; between 5 and 10% of patients develop an endocrinological disorder. In this article, we report a case of diabetic ketoacidosis prior to a diagnosis of type-1 diabetes mellitus, secondary to treatment with nivolumab.

Case Report

A 46-year-old male patient who presented with dyslipidemia as his only personal history (with no family history of type-1 diabetes mellitus) went to the emergency department due to abdominal pain associated with vomiting and nausea 48 hours previously. On physical examination, no sign of alarm was observed, except for slight dehydration of the skin and mucous membranes. Likewise, there were no signs of insulin resistance such as acanthosis nigricans, weight gain, or manifestations of metabolic syndrome. The patient's weight at the time of the emergency visit was 65 kg (height, 181 cm; body mass index [BMI], 19.84 kg/m²).

Four years previously, the patient had been diagnosed with stage-IV clear cell renal carcinoma with bilateral pulmonary metastatic involvement. This was treated with right radical nephrectomy and sunitinib, maintained for 24 months, until a reassessment. Computerized tomography (CT) showed a progression of the pulmonary and hepatic lesions, prompting treatment with nivolumab, and resulting in a complete response of the pulmonary lesions and partial liver damage.

Urgent blood and urine tests were performed as part of our evaluation (► **Table 1**) in which a picture of diabetic ketoacidosis could be seen. The patient's previous blood glucose levels had never been higher than 110 mg/dL (6.10 mmol/L) at any time, and he had not reported hyperglycemia symptoms

such as polydipsia, polyuria, or dyspnea. Treatment was started with bicarbonate, intravenous insulin, and fluid therapy in the medical oncology unit, with a good response (decrease in blood glucose levels and normalization of the pH and renal function values). During diabetic assessment, a glycosylated hemoglobin (HbA1C) of 9.4% and a C-peptide of 0.182 (nmol/L) were observed.

The patient presented good clinical evolution during admission, with normalization of blood glucose levels and disappearance of symptoms, given this good evolution, it was decided to discharge with insulin treatment, 16 units of insulin degludec basal, and insulin action rapid as part in a corrective pattern based on preprandial blood glucose levels.

Discussion

Endocrine side effects with treatments based on immunotherapy are observed in 5 to 10% of patients and can be severe in many cases.^{8,9} Pancreatic endocrine complications are described in 0.5 to 5% of cases. Alterations in baseline fasting glycemia and the development of type-1 diabetes are among the adverse effects described.¹⁰ These immunotherapies, when producing the inhibition of the pathways that lead to the arrest of T-cell activity, amplify the cellular immune activity, and the consequent increased immune response can lead to a destruction of the pancreatic β -cells.^{11,12} Diabetic ketoacidosis is a rare complication (in ~0.1% of patients) described in treatments with anti-PD-1 molecules. In our patient, we observed extremely low levels of C-peptide, which reflects the scarce pancreatic reserve of the patient at the time of diagnosis, which aggravated the debut and, ultimately, required insulin treatment at discharge. The HbA1C figure presented by the patient, 9.4%, correlated with a mean glycemia of 12.32 (mmol/L) in the 3 months prior to the analytical determination, demonstrating the rapid evolution of β -cell loss in the pancreas. The honeymoon period observed in young patients with a recent diagnosis of type-1 diabetes was not observed in our patients after discharge. The average time, described in the literature, from the administration of the first dose to the onset of symptoms is 14.6 weeks; however, in the case of our patient, it is 40 weeks. Likewise, the average dose of immunotherapy received in the literature for the appearance of symptoms is 5.3 doses, and in the case of our patient it has been 14 doses of nivolumab. The comments previously exposed, allows us to observe that in most cases the DMT1 develops in a short period of time, this does not happen in the case of our patient, which illustrates the need to follow-up beyond the average described in other cases reported.

In contrast to other endocrine complications, there is no clear established therapy for cases of type-1 diabetes mellitus secondary to treatment with immunotherapy. For example, in other side effects due to immunotherapy, treatment with corticosteroids is routine. However, in cases of type-1 diabetes, corticosteroids are typically avoided because of the fear of increasing the existing hyperglycemia. Thus, these patients are treated similarly to idiopathic type-1 diabetes patients.¹³

Table 1 Urgent blood and urine test

Determination	Results	Laboratory range
Glucose	32.03 (mmol/L)	3.89–5.55 (mmol/L)
Creatinine	0.21 (mmol/L)	0.06–0.11 (mmol/L)
FG (CKD-EPI)	32 (mL/min/1.73m ²)	≥90 (mL/min/1,73 m ²)
GAP anion plasma	38.23 (mmol/L)	8,00–16.00 (mmol/L)
pH	7.11	7.35–7.45
pCO ₂	22.00 (mm Hg) 2.93 (kPa)	35–45 (mm Hg) 4.67–6 (kPa)
Bicarbonate	7.00 (mmol/L)	26.00–32–00 (mmol/L)
GAD65 autoantibodies	1.6 (UI/mL)	0.0–5.0 (UI/mL)
IAA	1.3 (UI/mL)	0.0–0.4 (UI/mL)
IA-2 autoantibodies	3.6 (UI/mL)	0.0–0.8 (UI/mL)
Ketone bodies urine	>3.0 (mmol/L)	0.0–0.5 (mmol/L)
Glucose urine	>55.51 (mmol/L)	0.0–0.83 (mmol/L)

Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration; FG, glomerular filtration; GAD65, glutamic acid decarboxylase; IA-2, islet antigen-2; IAA, insulin autoantibodies.

Strict endocrine control is necessary during immuno-therapy treatment, as well as every 3 to 6 months after the immunotherapy has finished. It is recommended to monitor levels of basal glycemia,¹⁴ Thyroid stimulating hormone (TSH), free T4, basal cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone in men. However, there are no clear indications for the monitoring of pancreatic reserve levels or glycemic control, even though these patients develop hyperglycemia in an accelerated manner. For these reasons, we propose the need for closer and regular monitoring of C-peptide and HbA1c, which might avoid diabetic complications or arrest the development of type-1 diabetes mellitus.¹⁵

Conclusion

The appearance of endocrine side effects in the treatment based on immunotherapy, results in a significant number of complications, which can be in many cases of seriousness. The endocrine monitoring protocols in these patients have not been adapted to a pancreatic level. In accordance with the above, we propose the follow-up of these patients through the monitoring of the C-peptide and the HbA1c in every 2 months.

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None.

Conflict of Interest

None declared.

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