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CASO CLÍNICO

Immune-Mediated Diabetes Induced by Dostarlimab: A Case Report

Diabetes Imunomediada Induzida por Dostarlimab: Um Caso Clínico

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ABSTRACT

Immune checkpoint inhibitors (ICI), particularly antibodies targeting programmed death receptor-1 (PD-1) and its ligand, programmed death-ligand 1, have been rarely associated with the development of immune-mediated diabetes *mellitus*. To the best of our knowledge, we report the first published case of immune-mediated diabetes *mellitus* associated with dostarlimab—a monoclonal antibody targeting PD-1—in a 78-year-old woman diagnosed with endometrial adenocarcinoma and persistent peritoneal disease. Following six cycles of dostarlimab, she presented with diabetic ketoacidosis. Despite negative autoimmune antibodies, her relatively low HbA1c and C-peptide levels together with her clinical presentation were highly suggestive of ICI-induced diabetes *mellitus*. Following stabilization with intravenous fluids and insulin infusion, she was transitioned to a basal-bolus insulin regimen. Dostarlimab was discontinued, and restaging showed resolution of peritoneal disease. This case emphasizes the importance of early detection and management of ICI-induced diabetes *mellitus*.
Keywords: Diabetes Mellitus, Type 1/chemically induced; Endocrine System Diseases; Immune Checkpoint Inhibitors

RESUMO

Inibidores do *checkpoint* imunológico (ICI), particularmente anticorpos que têm como alvo a proteína de morte celular programada (PD-1) e o ligando 1 da proteína de morte celular programada, têm sido raramente associados ao desenvolvimento de diabetes *mellitus* imunomediada. Apresentamos, tanto quanto temos conhecimento, o primeiro caso publicado de DM imunomediada associada ao dostarlimab (anticorpo monoclonal que se liga ao PD-1), numa mulher de 78 anos com adenocarcinoma do endométrio e doença peritoneal persistente. Após seis ciclos de dostarlimab, a doente desenvolveu cetoacidose diabética. Apesar da negatividade dos autoanticorpos, os valores relativamente baixos de HbA1c e péptido C associados à apresentação clínica foram muito sugestivos de diabetes *mellitus* induzida por ICI. Após estabilização com fluidoterapia e perfusão de insulina, iniciou-se insulinoterapia em esquema basal-bólus. O tratamento com dostarlimab foi suspenso e a reavaliação revelou resolução da doença peritoneal. Este caso realça a importância da deteção precoce e tratamento adequado da diabetes *mellitus* induzida por ICI.
Palavras-chave: Diabetes Mellitus Tipo 1/induzida quimicamente; Doenças do Sistema Endócrino; Inibidores de Checkpoint Imunológico

INTRODUCTION

Immune checkpoint inhibitors (ICI) have transformed cancer therapy by enhancing T cell activation and strengthening the immune system's ability to eliminate tumor cells.[1] However, T-cell activation is non-specific and can trigger autoimmune adverse reactions.[2]

The main immune checkpoint pathways are cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein-1 (PD-1). Programmed cell death protein-1 binds to programmed cell death protein ligand-1 (PD-L1) to regulate immune response. Human pancreatic cells express PD-L1 to protect themselves from immune attack.[3]

Dostarlimab, a PD-1-blocking monoclonal antibody, disrupts this pathway, making pancreatic beta cells susceptible to immune-mediated destruction and potentially causing diabetes *mellitus* (DM), reported in ~ 0.2% of patients treated with monotherapy.[4]

We present, to the best of our knowledge, the first published case of immune-mediated DM associated with dostarlimab in a patient with metastatic endometrial adenocarcinoma.

CASE DESCRIPTION

The patient was a 78-year-old woman diagnosed with endometrial adenocarcinoma with lymph node metastasis and peritoneal carcinomatosis. She underwent surgery and subsequent chemotherapy and hormone therapy.

Due to persistent peritoneal disease, dostarlimab was initiated. No prior personal or family history of DM was noted. Her medical history included arterial hypertension and autoimmune thyroiditis. Endocrine evaluation, including blood glucose levels and thyroid function tests, was normal at baseline and at each dostarlimab cycle. Following six cycles of dostarlimab, during an urgent oncology appointment, the patient reported fatigue, polydipsia and polyuria over the preceding week. She

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was conscious and oriented, exhibiting tachypnea, fatigue with minimal exertion, and clinical signs of dehydration. Vital signs were stable and physical examination was unremarkable.

During observation, the patient experienced a syncopal episode with recovery within seconds. She also had two episodes of vomiting, with blood pressure decreasing to 84/48 mmHg. Arterial blood gas showed metabolic acidosis and severe hyperglycemia: pH 7.07 (7.35 - 7.45), pO2 105 mmHg (80 - 100), pCO2 10.5 mmHg (35 - 45), glucose 808 mg/dL, HCO3 6.5 mEq/L (22 - 26), lactate 3.40 mmol/L (0.5 - 1.5), anion gap 28.3 mmol/L (7 - 16). Serum ketones were 5.9 mmol/L (< 0.6).

She was diagnosed with diabetic ketoacidosis (DKA), referred to the emergency department and subsequently transferred to the Intensive Care Unit. Table 1 summarizes her blood test results, which revealed acute kidney injury and leukocytosis with neutrophilia. Septic screen (urine, blood cultures, chest X-ray) was unremarkable. Abdominal computed tomography (CT) scan showed no pancreatic masses.

The laboratory results for evaluation of DM are summarized in Table 2. The results showed an HbA1c of 7.6%, glucose 308 mg/dL, C-peptide 0.17 ng/mL (1.1 - 4.4) and the immunological blood tests for autoimmune diabetes (anti-islets of Langerhans antibodies, anti-insulin, anti-glutamic acid decarboxylase, and anti-zinc transporter) were negative.

She was diagnosed with ICI-induced DM and treated with intravenous fluids and continuous insulin infusion. Following the resolution of DKA and resumption of oral intake, she was transferred to the ward under the care of the Endocrinology department.

A basal-bolus insulin regimen was initiated, and a continuous glucose monitoring device was placed. After 18 days of hospitalization, the patient was discharged.

The patient maintained acceptable metabolic control, with an HbA1c of 7.8% at the last endocrinology appointment.

The oncology team decided to suspend dostarlimab and request restaging tests. A whole-body FDG PET/CT scan revealed resolution of peritoneal disease, with no new recurrence at other sites, suggesting a response to the treatment with dostarlimab. Adjuvant hormone therapy was proposed, but the patient preferred to remain under surveillance.

DISCUSSION

Dostarlimab has been approved for the treatment of advanced or recurrent endometrial cancer.[5]

It has been suggested that the PD-1 pathway plays a role in preventing the development of immune-mediated DM and blocking PD-1 or PD-L1 disrupts this immunoregulatory process.[6]

Owing to the rapid β cell dysfunction, the characteristic features of ICI-induced DM include a rapid onset, marked by a short period of hyperglycemia, often accompanied by relatively low HbA1c levels (7% - 8%), a low or undetectable C-peptide and a high incidence of DKA.[7-9] Islet autoantibodies are positive in about 50% of cases.

In the reported case, the presentation of DKA at diagnosis, along with relatively low levels of HbA1c and C-peptide, suggests that the patient's diabetes is most likely due to deficient insulin production from impaired beta cell function, like immune-mediated DM.

Due to its sudden onset, prompt diagnosis and intervention are essential to improve prognosis. Essential components of DKA management include continuous insulin infusion and aggressive fluid resuscitation.[10] Immune checkpoint inhibitor (ICI)-induced diabetes *mellitus* results in a permanent insulin-dependent state, even after discontinuation of ICI therapy.[11,12]

Guidelines from the European Society for Medical Oncology and the American Society of Clinical Oncology recommend withholding ICI therapy until the patient is clinically stabilized.[10,13] In our case report, the patient showed resolution of peritoneal disease and dostarlimab was not resumed.

Currently, there is a lack of a standard screening protocol. The American Society of Clinical Oncology recommends monitoring patients for hyperglycemia or other signs and symptoms of new or worsening DM by measuring glucose at baseline and at each treatment cycle during the first three months, then every three to six weeks thereafter.[13]

In the reported case, glucose monitoring was performed at each cycle, which was not sufficient for early detection of DM. Perhaps educating patients about the symptoms of hyperglycemia and DKA may play a significant role in the early detection of diabetes. Notably, the patient in the reported case experienced symptoms associated with hyperglycemia for one week.

In conclusion, ICI-induced DM is an uncommon, yet severe side effect of immunotherapy and healthcare professionals should carefully monitor blood glucose levels and alert patients to the symptoms of hyperglycemia.

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AUTOR CONTRIBUTIONS

AP: Writing of the manuscript.
BP, ML, AF: Critical review of the manuscript.
CC: Writing and critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients 'data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Table 1 – Laboratory results on day one of Intensive Care Unit

Blood test	Value	Reference range
Haemoglobin (g/dL)	12.7	12 - 15
Leucocytes ($x10^9$/L)	15.0	4 - 10
Neutrophils ($x10^9$/L)	12.6	1.5 - 8
Serum glucose (mg/dL)	775	74 - 106
Sodium (mmol/L)	132	136 - 145
Potassium (mmol/L)	5	3.5 - 5.1
Chloride (mmol/L)	89	98 - 107
Urea (mg/dL)	105	17 - 49
Creatinine (mg/dL)	1.67	0.5 - 0.9
Estimated glomerular filtratrion rate (mL/min/1.73 m^2)	31	> 90
C-reactive protein (mg/dL)	0.57	< 0.50
Procalcitonin (mg/dL)	0.05	< 0.1

Table 2 – Laboratory evaluation of diabetes *mellitus*

Blood test	Value	Reference range
Glucose (mg/dL)	308	74 - 106
HbA1c (%)	7.6	< 5.7
Peptide C (ng/dL)	0.17	1.1 - 4.4