Diabetes mellitus associated with immune checkpoint inhibitors

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Abstract

Introduction: immune checkpoint inhibitors (ICIs) have improved the prognosis of some cancers. However, immune adverse events have been reported, affecting different endocrine organs, including ICI-induced diabetes mellitus (ICI-DM). This is a rare adverse event, with a prevalence close to 2%, and occurs as type 1 DM (DM1) or worsening of type 2 DM (DM2). We present four cases of previously normoglycemic patients who developed new onset DM after immunotherapy.

Discussion: the diagnosis of ICI-DM is based on clinical presentation, the need for multiple doses of insulin, positive anti-islet cell or anti-glutamic acid decarboxylase (GAD) antibodies, a usual onset as DKA (in 67% of the cases), with low C-peptide levels, and rapid onset, which, in the presence of ICI, support the diagnostic suspicion.

Conclusions: these adverse events do not contraindicate the use of ICIs, but immunotherapy adjustments must be made by multidisciplinary groups. (Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3104).

Keywords: *immune checkpoint inhibitors; type 1 diabetes mellitus; clinical cases, neoplasms, immunotherapy.*

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Introduction

Immunotherapy has changed cancer treatment, activating the immune system to combat tumor cells, thus improving the host's immune response (1-4). Immune checkpoint inhibitors (ICIs) exert their effect by blocking the usual inhibitory pathways of T-cell regulation (5). Cytotoxic T lymphocyte antigen-4 (CTLA-4) receptors and programmed cell death protein-1 (PD-1) or its related ligand (PD-L1) are the target of these therapies (5). These include the anti-PD-1 antibodies: nivolumab, pembrolizumab and cemiplimab, the anti-PD-L1 antibodies: atezolizumab, avelumab and durvalumb, and the anti-CTLA-4 antibodies: ipilimumab and tremelimumab (6-8).

The ICIs have been approved for treating hematological neoplasms like Hodgkin lymphoma and solid tumors like squamous cell carcinomas of the head and neck, tumors with microsatellite instability, non-small cell tumors, lung cancer, renal cell carcinoma, melanomas, urothelial tumors and Merkel cell carcinomas, improving the survival rates, prognosis and survival of previously untreatable cancers (5). Between 60 and 95% of the patients have some side effect, involving the skin, gastrointestinal tract, endocrine system and liver (5). The incidence of serious events is 26% for monotherapy and up to 55% with combination therapy (CTLA-4 plus PD-L1/PD-1) (1, 2).

Among the side effects, endocrine disorders are the third most common cause. Diabetes associated with ICIs is rare, with an approximately 2% prevalence, occurring as type 1 diabetes mellitus (T1DM), with fulminant (rapid-onset) diabetes, or worsening of type 2 diabetes mellitus (T2DM). The classic symptoms are polydipsia, polyuria, polyphagia, and weight loss during immunotherapy (1, 2). Below, we present four cases of previously normoglycemic patients who developed diabetic ketoacidosis (DKA) after beginning immunotherapy and required multiple daily doses of insulin.

Cases

Case 1

A 56-year-old woman with a history of clear cell renal cell carcinoma restricted to the kidney, in stage pT1bNxM0 WHO/ISUP 1, treated with radical left nephrectomy and fractionated radiosurgery of a psoas muscle lesion, in whom local recurrence was documented in the surgical bed and psoas, seen on 18F-FDG PET. She had been on immunotherapy since 2021, initially with nivolumab plus ipilimumab for four cycles, and then nivolumab every 15 days. She was diagnosed with secondary adrenal insufficiency due to severe hyponatremia one year after beginning immunotherapy

and was therefore prescribed glucocorticoid replacement with prednisolone 5 mg/day. In addition, she had a history of osteoporosis with a high risk of fracture and stage 1A1 chronic kidney disease (CKD).

During her second year of immunotherapy, she was hospitalized for emesis coupled with diffuse abdominal pain, polydipsia and a 5 kg weight loss in two weeks. On admission, she was tachycardic and dehydrated, with a blood glucose level of 343 mg/dL and evidence of severe DKA, which was compatible with new-onset DM. She was started on a basal-bolus insulin treatment plan, and C-peptide and anti-GAD were ordered (Table 1). In light of her low C-peptide level, she was diagnosed with ICI-T1DM. During follow up, she presented wide blood glucose fluctuations and hypoglycemia and is therefore currently on intermittent continuous glucose monitoring (CGM) and being assessed for an insulin pump.

Case 2

A 19-year-old man with a history of familial leiomyomatosis (Reed's syndrome), an FH c575C>t gene mutation with renal cell carcinoma for which he underwent right nephrectomy in 2019, as well as CKD G1A1 (monokidney), secondary hypertension and mild obstructive sleep apnea (OSA), with evidence of hypermetabolic lymph node and bone metastases on 18F-FDG PET. He received oncological treatment with bevacizumab and erlotinib in 2019, subsequently changing to axitinib until 2020 and, after progression, changing to nivolumab from April 2021 to September 2022 (12 cycles).

In the course of his disease, one month after beginning ICIs, after the second dose of nivolumab, he developed polydipsia, polyuria, and weight loss. On admission, he had a blood glucose level greater than 400 mg/dL, with moderate DKA that required ICU care. He had a decreased C-peptide and was positive for anti-GAD65 (Table 1). Basal-bolus insulin treatment was ordered, with poor metabolic control indicated by glycemic excursions, and he was therefore started on intermittent CGM and carbohydrate counting, with which he achieved 72% time in range, 24% time above range and 24% time below range, with low glycemic variability.

Case 3

A 58-year-old man with a history of metastatic malignant melanoma with no visible skin lesions, initially diagnosed in May 2022, with documented lung, liver, bone and retroperitoneal metastases. Immunohistochemistry studies showed non-mutated BRAF, and he was given first-line oncological treatment with nivolumab plus ipilimumab in August 2022, receiving four cycles. He subsequently presented with a blood glucose level of 527 mg/dL, along with polydipsia and polyuria, with no other comorbidities, and initial laboratory tests (Table 1) which ruled out an acute hyperglycemic crisis. He was diagnosed with T1DM and started on a basal-bolus insulin plan, with good metabolic control during hospitalization. His C-peptide is pending. Due to his clinical presentation, he was considered to have ICI-T1DM.

Case 4

An 85-year-old woman with a history of acral lentiginous melanoma diagnosed in 2014, who was initially treated surgically with disarticulation. She subsequently progressed to lung, small intestine and central nervous system metastases in 2017. Oncological treatment with nivolumab was ordered, with 11 cycles completed from 2018 to May 2019.

In December 2018, she debuted with mild DKA, with an HbA1c of 9.6%. She was prescribed ambulatory treatment with a basal-bolus insulin plan. In July 2019, she was hospitalized for level III hypoglycemia and high variability, and her treatment was therefore adjusted to a second-generation basal insulin analogue and an SGLT2 inhibitor.

In October 2019, she had an episode of severe DKA requiring ICU care and invasive mechanical ventilation, which was triggered by viral gastroenteritis. The episode resolved and she was once again discharged with a basal-bolus plan without SGLT2 inhibitors.

She restarted her immunotherapy (with nivolumab) in January 2020, and was hospitalized in May 2023 for hyperglycemia without decompensation, with high variability and unnoticed episodes of hypoglycemia. Her basal-bolus plan dose was adjusted, and intermittent CGM was begun. C-peptide and anti-GAD measurement are pending, for suspected ICI-T1DM.

Discussion

The clinical presentation of ICI-DM is rare, with a prevalence of 2%. It tends to present as new-onset T1DM, and sometimes as worsening T2DM (1, 2). In our series, we describe previously normoglycemic patients with ages ranging from 19 to 85, who developed hyperglycemia after ICI. Pancreatic involvement is more common with the use of PD-1 and PD-L1, or in combination with CTLA-4 (2). In our case series, all the patients were being treated with PD-1/PD-L1, and two of them were on combination therapy with CTLA-4, supporting what is found in the literature (1–5). The ICI-DM mechanism is not entirely clear; it seems to be similar to the T1DM autoimmune process, with more rapid and aggressive lymphocyte-mediated destruction of the pancreatic beta cells (5, 9). A genetic predisposition has been reported in up to 70% of the patients who develop ICI-T1DM (1, 5). Other more common causes of hyperglycemia, like steroid use, should always be ruled out (1, 5).

Regarding ICI-DM's clinical presentation, beta cell failure symptoms (polydipsia, polyuria and weight loss) stand out (1,5), and up to two-thirds of patients debut with DKA. Hyperglycemia appears between the seventh and seventeenth week after beginning ICI, with some reports up to years later (5), and it is generally considered to be an early complication of ICIs (8, 9). Just as reported in the literature,

Table 1. *Clinical and paraclinical information.*

Clinical Information	Case 1 patient	Case 2 patient	Case 3 patient	Case 4 patient
Age	56 years	19 years	58 years	85 years
HbA1C at diagnosis	8.4%	8.5%	13.8%	9.6%
BMI	Overweight	Normal	Overweight	Normal
Use of steroids during immunotherapy	No	No	No	No
Type of immunotherapy	Nivolumab+ipilimumab	Nivolumab	Nivolumab+ ipilimumab	Nivolumab
C-peptide levels (0.9 - 7.1 ng/ml)	<0.10 ng/mL	0.05 ng/mL	No data	No data
Anti-GAD antibodies (<1 U/mL)	No data	650.4 U/mL (Positive)	No data	No data
Beta cell failure symptoms	YES	YES	No	YES
Onset of hyperglycemia after immunotherapy	96 weeks	4 weeks	20 weeks	24 weeks
Debut as DKA	Yes	Yes	No	Yesi
Total daily insulin dose IU/ kg	0.4	0.6	0.5	0.3
Continuous insulin monitoring	FreeStyle	FreeStyle	No	FreeStyle

Source: Prepared by the authors

our patients debuted with hyperglycemia after ICI, within a variable range (4-96 weeks).

Patients with rapid pancreatic tissue destruction present with moderate to severe hyperglycemia, low or absent serum C-peptide, and mildly elevated HbA1 glycosylated hemoglobin (HbA1c) (explained by the rapid onset of the disease) (5), unlike the cases of worsening DM, in which the glycosylated hemoglobin may be higher (5-8). Only half of the patients have anti-pancreatic islet cell and anti-GAD antibodies, which are important to help distinguish between type 1 and type 2 DM (5, 9). In our series, one patient was anti-GAD positive and two had suppressed C-peptide, with data lacking for the rest. Analyzing the clinical behavior of Cases 1, 2 and 4, who debuted with DKA, required insulin beginning at diagnosis, and had high glycemic variability and hypoglycemias, we believe that they are very suggestive of T1DM. In contrast, Case 3 presented hyperglycemia without decompensation, no variability or hypoglycemia, in addition to a higher HbA1c, which suggests less beta cell destruction.

Given the aggressive pathophysiology of the disease, insulin therapy is started early, with higher doses in patients on steroids (5). When the presentation occurs during a DKA episode, the recommendation is to discontinue immunotherapy until the symptoms are controlled. On the other hand, in patients with mild hyperglycemia or with pre-existent T2DM, treatment may continue uninterrupted, with the appropriate pharmacological adjustments (2, 8, 9). All of our patients restarted ICI therapy after normalizing their blood sugars.

Fulminant diabetes (FD) is described as the simultaneous presence of DKA, an initial glucose level greater than 228 mg/dL, HbA1c less than 8.7%, basal C-peptide less than 0.3 ng/mL or postprandial C-peptide less than 0.5 ng/m, rapid beta cell destruction, and elevated lipase and amylase in 98% of the patients, suggesting related exocrine pancreatic involvement, with rapid onset of the symptoms in up to 59% of cases (1). In this series, Case 3 met the critera for FD.

Conclusions

Immune checkpoint inhibitor-induced diabetes mellitus is rare and generally debuts with insulinopenia. There are no reports of diabetes remission when treatment is discontinued, negatively impacting the patients' quality of life, as they require additional treatments beyond those for cancer, such as multiple-dose insulin schemes, glucose monitoring and specialized follow up. This adverse effect is not an absolute contraindication to continuing ICIs. To date, the onset of endocrine disorders associated with ICIs has not been shown to be associated with better tumor response to therapy.

Patient perspective

The patients expressed their concern regarding the adverse effects of immunotherapy and their need for more information and education on these effects.

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