Picón César, María José. Hospital Universitario Virgen de la Victoria [Virgen de la Victoria University Hospital], Málaga.

Rubio García, José Antonio. Hospital Universitario Príncipe de Asturias [Príncipe de Asturias University Hospital], Alcalá de Henares-Madrid.

Soldevila Madorell, Berta. Hospital U. Germans Trias i Pujol [Germans Trias i Pujol University Hospital], Badalona - Barcelona.

Vega Guedes, Begoña. Complejo Hospitalario Universitario Insular Materno-Infantil [Island Mother and Child University Hospital Complex], Las Palmas, Las Palmas.

Vinagre Torres, Irene. Hospital Clínico y Provincial de Barcelona [Clinical and Provincial Hospital of Barcelona], Barcelona.

Wägner Falhin, Ana María. Complejo Hospitalario Universitario Insular Materno-Infantil [Island Mother and Child University Hospital Complex], Las Palmas, Las Palmas.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.endinu.2022.07.005.

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María M. Goya[a,*], Marta Miserachs[b], Mercè Codina[c], Irene Vinagre[d], on behalf of the GEDE

[a] *Servicio de Obstetricia y Ginecología, Fundación Althaia, Hospital de Manresa, Barcelona, Spain*
[b] *Servicio de Obstetricia y Ginecología, Hospital Vall d'Hebron, Barcelona, Spain*
[c] *Servicio de Endocrinología, Hospital Son Espasses, Palma de Mallorca, Spain*
[d] *Servicio de Endocrinología, Hospital Clínico y Provincial de Barcelona, Barcelona, Spain*

Corresponding author.
E-mail address: maria.goya@vhir.org (M.M. Goya).

Abrupt-onset diabetes mellitus secondary to pembrolizumab

Diabetes mellitus de comienzo abrupto secundaria a pembrolizumab

Over recent years, immunotherapy has been increasingly used to treat several types of cancer. Its aim is to present an immune response against the tumour through monoclonal antibodies that inhibit immune checkpoints. These include drugs that inhibit the PD-1 ligand (PD-L1), cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors and others, such as pembrolizumab and nivolumab, which inhibit the programmed cell death receptor 1 (PD-1) on the surface of T cells. As side effects, they can cause autoimmune disorders in many organs of the endocrine system and beyond, including hypophysitis, thyroiditis, adrenalitis and diabetes mellitus (the latter two are rarer).[1] We report a case of sudden-onset diabetes mellitus at our centre following treatment with pembrolizumab.

Our patient was a 74-year-old woman whose only history of relevance was pT2aN0M0 nodular melanoma (stage IB) in the right pretibial region in 2009 that was surgically treated. She had a recurrence in 2015 in the form of a 5-mm skin metastasis, which was removed, and a second recurrence in 2019 with two metastatic lesions contiguous to the graft, multiple lung metastases as well as metastases in the subcutaneous cellular tissue of the right axillary region and chest wall, at which point treatment was started with seven cycles of pembrolizumab every 21 days for six months. The last cycle was 19 days before she attended the Accident and Emergency department. She came to the Accident and Emergency department due to a 48-h history of general malaise, asthenia, dry mouth, polyuria, polydipsia, abdominal pain and vomiting. Her last basal blood glucose

Table 1 Lab test parameters.

Parameter	Value	Reference range
Glucose (mg/dl)	558	74–100
Sodium (mEq/l)	122	132–146
Potassium (mEq/l)	4.9	3.5–5.5
HbA1c (%)	8.6	4–6
pH	6.84	7.31–7.41
Bicarbonate (mmol/l)	3.6	24–28
Ketonaemia (mmol/l)	6	<0.6
Glomerular filtration rate (ml [min/1.73 m^2])	51	0.0–9,999.9
Leukocytes ($\times 10^3$ μl)	29,700	4,500–11,000
CRP (mg/dl)	1.40	0.00–0.50
Stimulated C-peptide (ng/mL)	0.15	1.1–4.4
Anti-GAD	Negative	0.00–0.75
Anti-IA2	Negative	0.00–0.75
Anti-ICA	1.5	0.00–0.75

measurement was 89 mg/dl two months prior. Upon arrival at Accident and Emergency, her blood glucose was 558 mg/dl, with pH 6.84, bicarbonate 3.6 and ketonaemia 6 mmol/l. She was admitted to the intensive care unit due to severe diabetic ketoacidosis, where she was prescribed fluid therapy and intravenous insulin. Once stable, she was transferred to the endocrinology ward. Glycated haemoglobin (HbA1c) was 8.1%. Stimulated C-peptide was 0.15 ng/mL. The patient was negative for anti-GAD and anti-IA2 antibodies but positive at low titres for anti-pancreatic islet cell antibodies. The other complementary tests (chest X-ray, electrocardiogram) were normal. She was discharged with a basal-bolus insulin regimen. The data for our patient are shown in Table 1.

To date, dozens of cases of diabetes mellitus secondary to immunotherapy have been reported. It is a rare condition accounting for just 1% of the endocrine disorders that immunotherapy can cause.[2]

Pembrolizumab is approved for melanoma, metastatic non-small cell lung cancer, metastatic or recurrent head and neck cancer and refractory Hodgkin's lymphoma. Most cases of immunotherapy-induced diabetes are caused by melanomas, the majority of which are treated with pembrolizumab.[1,3] The diagnostic criteria proposed by the Japan Diabetes Society are used: onset of diabetic ketosis or ketoacidosis approximately seven days after the onset of hyperglycaemia, glucose level $\geq$288 mg/dl and HbA1c <8.7% at the first visit, and fasting serum C-peptide level <0.3 ng/mL.[4] Most (66–70%) initially manifest fulminant symptoms in the form of diabetic ketoacidosis with elevated blood glucose (including in excess of 700 mg/dl[5]) and only slightly elevated HbA1c, suggestive of sudden onset.[2,3] C-peptide levels are usually low or undetectable. Pancreatic lipase levels are typically elevated in 52% of patients,[2] although this was not measured in our patient. It is irreversible in most cases. There is usually no clear predominance of one gender over another. Pancreatic autoimmunity is positive in 39–53% of cases,[2,6] particularly anti-GAD. This differs from classic type 1 diabetes mellitus (T1DM) in which antibody positivity is reported in more than 90% of cases. Other differences with T1DM include its more sudden onset in cases secondary to immunotherapy and older mean age (61 years) in these cases.

The use of glucocorticoids has been shown to be ineffective in slowing disease progression.[7] Risk is higher in patients previously administered another immunotherapy[3] or receiving combination therapy. Patients who have previously had another endocrine disorder secondary to immunotherapy or who have HLA predisposing to T1DM are also at increased risk.[2,3] Pre-existing type 2 diabetes mellitus (T2DM) does not increase the risk of manifesting this condition.

Diabetes mellitus secondary to immunotherapy is more common with PD-1 or PD-L1 inhibitors (and even more so when combined) than with anti-CTLA-4.[8] Onset varies from a few weeks after drug administration, sometimes even after the first or second immunotherapy cycle, to more than a year after starting immunotherapy.[8,9] Mean onset is four to five months after starting treatment or four cycles.[10]

While not very prevalent, diabetes secondary to immunotherapy is extremely severe. Use of immunotherapy is increasing and patients should be informed of the possible symptoms of ketoacidosis. In addition, the provision of a glucometer should be considered so that capillary blood glucose can be periodically monitored at least once every treatment cycle, enabling clinicians to detect the disease when hyperglycaemia is mild in order to prevent acute complications.

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Adrián Pastor Alcaraz*, Luis Marín Martínez, Georgios Kyriakos, María C. Álvarez Martín, Enrique Hernández Alonso

Servicio de Endocrinología y Nutrición, Hospital General Universitario Santa Lucía, Cartagena, Spain

* Corresponding author.
E-mail address: adri_v_a@hotmail.com (A. Pastor Alcaraz).