Endocrinología, Diabetes y Nutrición 68 (2021) 363–365

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Diabetes mellitus associated with immune checkpoint inhibitors treatment: A clinical case by atezolizumab☆

Diabetes mellitus asociada al tratamiento con inhibidores de puntos de control inmune: un caso clínico con atezolizumab

Dear Editor,

In recent times, immunotherapy has taken on an expanding role in cancer treatment, thanks to its positive results compared to classic chemotherapy regimens. However, secondary immune-related adverse events (irAEs) can develop as a result of the alteration of immune tolerance in healthy peripheral tissues.[1] We report a case of diabetes mellitus (DM) associated with atezolizumab (a PD-L1 inhibitor), a rare occurrence in routine clinical practice.

This was an 82-year-old man diagnosed with stage IV lung adenocarcinoma (bilateral neoplastic lesions and prevascular mediastinal lymphadenopathy, T4N2M1a) treated with atezolizumab monotherapy (1200 mg every 21 days). In his physical examination and pre-treatment hormonal screening, he was recorded to have a weight of 78 kg, a BMI of 26.8 kg/m^2 and an ECOG performance status of 0, with no abnormalities in his thyroid profile or blood glucose control. He was not found to have any other significant personal or family history with regard to DM, dyslipidaemia, hypertension or anything else. He was not on treatment with corticosteroids or any other additional drugs.

Twenty-four weeks from the start, the patient visited the hospital emergency department with a three-day history of asthenia, polyuria and polydipsia, along with severe asthenia and confusion. Tests showed blood glucose 1078 mg/dl, arterial pH 7.22 with anion gap 16 mEq/l, lactic acid 2.3 mmol/l and urine positive for ketone bodies (equivalent to 30–40 mg/dl). The patient's creatinine and urea had increased to 1.98 mg/dl and 96 mg/dl, respectively (previously 0.96 mg/dl and 24 mg/dl). No abnormalities suggestive of exocrine pancreatic involvement were detected. The clinical impression was of new-onset diabetes with severe diabetic ketoacidosis along with secondary acute kidney injury.

The patient's condition was stabilised within 48 h and he was referred to the Diabetes Day Hospital (DDH), where he received basic diabetes education and was started on subcutaneous insulin therapy in a basal-bolus regimen (42 U/24 h, 0.54 U/kg/24 h). Over the following 15 weeks, the patient had five check-up appointments at the DDH coordinated with the Oncology department. He was subsequently referred to the Diabetes Outpatient Clinic for follow-up.

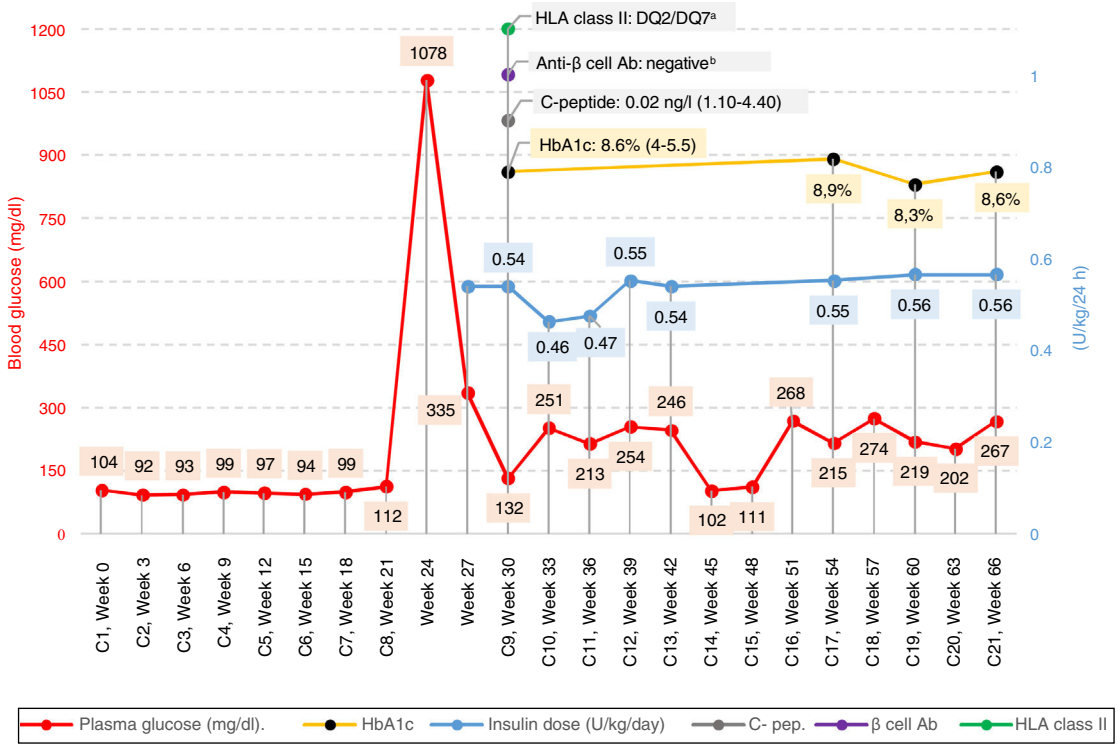
With a suspected diagnosis of atezolizumab-induced DM, the investigation was broadened to include measurement of C-peptide (0.02 ng/l), HbA1c (8.6%, 70 mmol/mol), anti-β-cell antibodies (with a negative result) and genetic determination of risk HLA class II (with a positive result for DQ2).[2] The results and changes over time in laboratory values are shown in Fig. 1.

The patient's insulin requirements did not subsequently significantly decrease over the course of follow-up. Currently, his suboptimal metabolic control persists (HbA1c >8.5%). In oncology follow-up, no tumour progression was found and he had no thyroid or cardiovascular problems (diabetes of recent onset).

Atezolizumab is an anti PD-L1 monoclonal antibody of the immune checkpoint inhibitor (ICI) family approved for the treatment of breast, urothelial and non-small cell lung cancer.[3] Its mechanism of action is aimed at blocking membrane proteins (PD-1, PD-L1 or CTLA-4) that trigger inhibitory signals in T lymphocytes, with the goal of increasing their ability to act against cancer cells. Because immune control mechanisms are altered, endocrine irAEs (especially thyroid) are common.[4] However, the development of ICI-induced DM (ICI-DM) is very rare (estimated incidence 0.2%–1.4%).[5] The only report in Spain we were able to find was a 2019 case report by León et al.[6] in relation to durvalumab.

The time of onset from the start of treatment is variable, with a median of around 15–20 weeks. ICI-DM has specific characteristics that distinguish it from other forms of autoimmune DM. It develops suddenly, often with ketoacidosis (71%) and C-peptide levels close to 0 (persistent insulin deficiency), which makes it difficult to predict. In our case, in week 21 a blood glucose level of 112 mg/dl was detected

☆ Please cite this article as: de Vera Gómez PR, Tous Romero MC, Portillo CM, Olmedo IS, Brocca MAM. Diabetes mellitus asociada al tratamiento con inhibidores de puntos de control inmune: un caso clínico con atezolizumab. Endocrinol Diabetes Nutr. 2021;68:363–365.



[a]HLA class II: DQ allele: DQ2 (DQ A1* 05:01–DQB1* 02:01) DQ7 (DQ A1*020 1-DQB1* 0301). DR allele not available.

[b]Anti-pancreatic islet cell antibodies (ICAs) dilution <1/5 (negative), anti-glutamic acid decarboxylase 65 (GAD65): 5.82 U/ml (0.0-17.0), anti-insulin antibodies (AIAs): 7.9 U/ml (0.0-20.0), anti-tyrosine phosphatase antibodies similar to insulinoma-associated antigen 2 (IA2): 6.87 U/ml (0.0-27.0). Anti-zinc transporter 8 (ZnT8): Not available.

Figure 1 Timeline and changes over time in laboratory values. Results are included according to the atezolizumab cycle number and treatment week.

[a] *HLA class II*. DQ allele: DQ2 (DQA1*05:01-DQB1*02:01) DQ7 (DQA1*0201-DQB1*0301). DR allele not available.

[b] *Anti–β-cell antibody.* Anti-pancreatic islet cell antibodies (ICAs) dilution <1/5 (negative), anti-glutamic acid decarboxylase 65 (GAD65): 5.82 U/mL (0.0–17.0), anti-insulin antibodies (AIAs): 7.9 U/mL (0.0–20.0), anti-tyrosine phosphatase antibodies similar to insulinoma-associated antigen 2 (IA2): 6.87 U/mL (0.0–27.0). Anti-zinc transporter 8 (ZnT8): Not available.

in a routine test and was not considered clinically significant (Fig. 1). This would suggest that, should slight abnormalities in blood glucose levels be detected, it could be beneficial to start the diagnostic process early.

In ICI-DM, there are no transitory remission periods (''honeymoon periods''), and insulin requirements remain constant over time. By contrast, in type 1 DM and latent autoimmune diabetes in adults (LADA), periods of up to two years with normal C-peptide levels are common.[7] HbA1c levels may be normal at diagnosis due to the rapid development of the disease (in our case, the determination was made 8 weeks after onset).[8] These characteristics are similar to fulminant DM in Asian populations, so they could share pathophysiological mechanisms.[9]

While in type 1 DM over 90% of cases are positive for at least one anti-β-cell antibody, in ICI-DM this has only been found in 50%, with anti-GAD65 being the most common.[8] In addition, Stamatouli et al.[10] suggested an association between the presence of the HLA class II-DR4 allele and the development of ICI-DM. Other risk haplotypes for type 1 DM that might predispose an individual to ICI-DM are DR4/DQ8 and DR3/DQ2, although a larger number of cases must be studied to confirm that relationship.[5,8]

For the follow-up of patients starting treatment with ICI, periodic blood glucose determinations could be useful, along with detailed information for the patient about suggestive symptoms, and mechanisms in place for early consultation should any of those symptoms appear. There is no consensus on systematic HbA1c and anti-β cell antibody screening because of their apparent low predictive value, despite the fact that they are the tests of choice in classic forms of DM and can add value once the event has occurred.[5,8] The determination of pancreatic markers of exocrine damage (such as pancreatic lipase), elevation of which has been demonstrated in up to 90% of cases of fulminant DM in Asian populations, could also be considered.[8,9]

Despite the low incidence of ICI-DM, the number of cases will most likely increase over the coming years with the gradual expansion of the use of these drugs in routine clinical practice. Consequently, we find it essential not only to know about ICI-DM, but also to report it so that multidisciplinary management strategies involving Oncology and Endocrinol-

ogy may be planned. For this purpose, we propose the DDH model as an optimal resource.

Authorship

All the authors declare that they contributed substantially to the concept of the study, drafting of the manuscript and approval of the submitted version of this article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Ferrari S, Fallahi P, Elia G, Ragusa F, Ruffilli I, Patrizio A, et al. Autoimmune endocrine dysfunctions associated with cancer immunotherapies. Int J Mol Sci. 2019;20:2560, http://dx.doi.org/10.3390/ijms20102560.
2. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. Nat Rev Endocrinol. 2019;15:635–50, http://dx.doi.org/10.1038/s41574-019-0254-y.
3. Agencia española de medicamentos y productos sanitarios. Informe de Posicionamiento Terapéutico de atezolizumab (Tecentriq®) en el tratamiento de cáncer de pulmón no microcítico. Madrid; 2018 [Cited June 2020]. Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-atezolizumab-Tecentriq-cancer-pulmon.pdf?x17133.
4. Dai S, Jia R, Zhang X, Fang Q, Huang L. The PD-1/PD-Ls pathway and autoimmune diseases. Cell Immunol. 2014;290:72–9, http://dx.doi.org/10.1016/j.cellimm.2014.05.006.
5. Quandt Z, Young A, Anderson M. Immune checkpoint inhibitor diabetes mellitus: a novel form of autoimmune diabetes. Clin Exp Immunol. 2020;200:131–40, http://dx.doi.org/10.1111/cei.13424.
6. León Mengíbar J, Capel I, Bonfill T, Mazarico I, Casamitjana Espuña L, Caixàs A, et al. Simultaneous onset of type 1 diabetes mellitus and silent thyroiditis under durvalumab treatment. Endocrinol Diabetes Metab Case Rep. 2019;2019, http://dx.doi.org/10.1530/EDM-19-0045.
7. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, et al. Fall in C-peptide during first 2 years from diagnosis: Evidence of at least two distinct phases from composite type 1 diabetes trialnet data. Diabetes. 2012;61:2066–73, http://dx.doi.org/10.2337/db11-1538.
8. de Filette J, Pen J, Decoster L, Vissers T, Bravenboer B, Van der Auwera B, et al. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol. 2019;181:363–74, http://dx.doi.org/10.1530/EJE-19-0291.
9. Murase-Mishiba Y, Imagawa A, Hanafusa T. Fulminant type 1 diabetes as a model of nature to explore the role of C-peptide. Exp Diabetes Res. 2008;2008:819123, http://dx.doi.org/10.1155/2008/819123.
10. Stamatouli A, Quandt Z, Perdigoto A, Clark P, Kluger H, Weiss S, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes. 2018;67:1471–80, http://dx.doi.org/10.2337/dbi18-0002.

Pablo Rodríguez de Vera Gómez*, María del Castillo Tous Romero, Cristóbal Morales Portillo, Isabel Serrano Olmedo, María Asunción Martínez Brocca

Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen Macarena, Sevilla, Spain

* Corresponding author.
E-mail address: pablordevera@gmail.com
(P. Rodríguez de Vera Gómez).