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REVIEW: ABOUT A CASE

Pembrolizumab-induced dual endocrine disruption: A case report

María Carmen Dameto Pons*, Elena González Arnáiz, María Antequera González, Xavier F. Pérez Candel, Diana Ariadel Cobo, Javier Castañón Alonso, María D. Ballesteros Pomar

Servicio de Endocrinología y Nutrición, Complejo Asistencial Universitario de León, Gerencia de Salud de Castilla y León (SACYL), Altos de Nava s/n, 24071 León, Spain

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Abstract Immunotherapy is an increasingly used treatment for different types of cancer. The most widely used are cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, PD-1 ligand (PD-L1) inhibitors and PD-1 receptor inhibitors. All of them can produce endocrine autoimmune side effects in multiple organs. The most frequent are thyroid disorders and hypophysitis although, less frequently, they can also cause autoimmune adrenalitis and autoimmune diabetes. Thyroid involvement is usually transient but can become chronic in the form of hypothyroidism in more than 50% of cases. Diabetes is due to autoimmune destruction of pancreatic β-cells, in many cases abrupt and irreversible. The 2 entities occur more frequently with PD-1 or PD-L1 inhibitors. This is the case of a patient with cutaneous melanoma on pembrolizumab who simultaneously developed thyroiditis and fulminant autoimmune diabetes.
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PALABRAS CLAVE
Diabetes autoinmune;
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Inmunoterapia;
Pembrolizumab

Disrupción endocrina dual inducida por pembrolizumab: reporte de un caso

Resumen La inmunoterapia es un tratamiento cada vez más utilizado para distintos tipos de cáncer. Los más empleados son los inhibidores del antígeno 4 de los linfocitos T citotóxicos (CTLA-4), los inhibidores del ligando del PD-1 (PD-L1) y los inhibidores del receptor PD-1. Todos ellos pueden producir efectos secundarios autoinmunes endocrinos en múltiples órganos. Los más frecuentes son los trastornos tiroideos y la hipofisitis, aunque, con menor frecuencia, también pueden provocar adrenalitis y diabetes autoinmune. La afectación tiroidea suele ser transitoria, pero puede hacerse crónica en forma de hipotiroidismo en más del 50% de los casos.

* Corresponding author.
E-mail address: carmendameto@gmail.com (M.C. Dameto Pons).

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La diabetes se debe a la destrucción autoinmune de las células β pancreáticas, muchas veces de forma abrupta e irreversible. Ambas entidades suelen presentarse con los inhibidores del PD-1 o del PD-L1. Este es el caso de un paciente con melanoma cutáneo a tratamiento con pembrolizumab que desarrolló, concomitantemente, tiroiditis y diabetes autoinmune fulminante.
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Case description

This is the case of a 67-year-old woman with a past medical history of high blood pressure on amlodipine 5 mg and total hysterectomy. In February 2024 she was diagnosed with lumbar melanoma BRAF V600E/E2/D mutated, pT3b pN2 cM0, stage IIIC. Both inguinal regions were explored by ultrasound and several subcentimetric lymph nodes were identified. Two of them were resected; one had melanoma metastases with multiple nests. Initially, surgical excision was performed in March 2024 followed by adjuvant treatment with immunotherapy with pembrolizumab 200 mg every 3 weeks for 1 year since May 2024. Prior to receiving the third cycle, the patient reported a 2-week history of general malaise and weight loss, which she attributed to the start of immunotherapy; however, for the last 5 days she had been experiencing polyuria and polydipsia with nausea and vomiting. Physical examination revealed pallor and mucocutaneous dryness, and fine distal tremor.

The patient was referred to the emergency department for assessment. The last baseline blood glucose level had been 96 mg/dL 2 months prior. Emergency laboratory tests showed glycemia of 374 mg/dL and positive ketone bodies, pH 7.25 (7.35–7.45) and HCO_3 14.1 mmol/L (23–25). With a diagnosis of diabetic ketoacidosis, she was admitted to the Oncology Department and rapidly referred to the endocrinologist for further management. Treatment started with a 12-h regimen of fluid therapy and IV insulin, followed by subcutaneous insulin as a basal bolus (0.6 IU/kg/day), and IV treatment was discontinued. Regular blood tests showed HbA1c 7.8%, C-peptide 0.648 ng/mL (>0.7), anti-GAD antibodies 506.9 U/mL (0–10), T4L 3.33 ng/dL (0.92–1.68) and TSH <0.005 microIU/L (0.27–4.20). Due to the finding of primary hyperthyroidism, anti-receptor antibodies (TSI) were requested to make the differential diagnosis between Graves' Basedow disease (GBS) and thyroiditis. With the diagnosis of fulminant diabetic debut due to pembrolizumab and hyperthyroidism pending diagnosis, treatment was prescribed with subcutaneous basal bolus insulin (26 IU of insulin glargine U300 and 9 IU of insulin lispro before each main meal) and antithyroid drugs (metimazol 5 mg/8 h).

An appointment was made by our department for a 2-week follow-up to assess if dose adjustment was required. At the same time the required documentation was processed to initiate a continuous glucose monitoring (CGM) program. Follow-up blood tests showed levels of T4L 0.4 ng/dL (0.92–1.68), T3L 0.164 ng/dL (0.2–0.44) and TSH 16.03 microIU/L (0.27–4.20), and treatment with methimazole 5 mg was discontinued 10 days after being prescribed.

In our next review, 3 weeks later, lab test results were T4L 0.2 ng/dL (0.92–1.68), T3L 0.116 ng/dL (0.2–0.44) and TSH 53.7 microIU/L (0.27–4.20). At this point the patient was in a hypothyroid phase, and it was decided to start low dose levothyroxine; 25 mcg daily until new control. Graves' disease was ruled out after obtaining negative anti-TSI antibodies and the diagnosis of pembrolizumab-induced autoimmune thyroiditis with posterior change to hypothyroidism was confirmed. During the third review, the CGM data showed that the patient had high glycemic variability (CV, 41.7%), mainly due to hypoglycemic corrections. Occasionally, nocturnal hypoglycemia occurred due to inaccurate carb counting and improper insulin lispro adjustment. The patient had GMI (Glucose Management Indicator) of 6.7%, mean glucose value of 143 mg/dL, time in range (TIR) 70–180 mg/dL of 69%, time above range (TAR) >180 mg/dL of 26% and time below range (TBR) <70 mg/dL of 5%, without severe hypoglycemia <54 mg/dL. Based on this information, it was decided to adjust the regimen to insulin glargine U300 30 IU and insulin lispro 8 IU before breakfast and lunch, and 6 IU before dinner. Levothyroxine was increased to 112 mcg daily (1.8 mcg/kg). In November, at the last consultation, she exhibited T4L values of 1.55 ng/dL (0.92–1.68), TSH 0.1 microIU/L (0.27–4.20), less glycemic variability (CV 32. 7%), GMI 7.2%, mean glucose value 163 mg/dL, TIR 70–180 mg/dL 61%, TAR >180 mg/dL 38% and TBR <70 mg/dL 1%, with no severe hypoglycemia <69 mg/dL. With these results, levothyroxine 100 mcg daily and insulin glargine U300 28 IU and insulin lispro 5 IU before breakfast, 7 IU before lunch and 3 IU before dinner were prescribed.

Management and evidence

Immunotherapy may induce endocrine adverse effects such as thyroid disease, hypophysitis, adrenal insufficiency and diabetes. It is therefore important to closely monitor and warn the patient of the associated symptoms.[1]

Immunotherapy-induced diabetes is a complication that occurs more frequently in patients on anti-PD-1/PD-L1 monoclonal antibodies such as pembrolizumab.[2] The incidence rate is estimated at around 1%–2% with this type of monoclonal antibodies and even higher with combined immunotherapy.[3] The main symptoms are polyuria, polydipsia and weight loss, although patients may also report intense asthenia or blurred vision.[2,3] Diagnosis is based on clinical suspicion and lab test results such as hyperglycemia,

ketonemia or ketonuria, acidosis, elevated HbA1c, low C-peptide levels and positive specific autoimmunity. Initial treatment is fluid therapy and IV insulin in moderate/severe cases and then subcutaneous insulin with a basal bolus regimen.[4]

Fulminant DM due to immunotherapy is a rare entity (1%) and is usually irreversible.[5] Clotman et al. evaluated a total of 42 cases of PD-1 inhibitor-induced DM and concluded that the median age at diagnosis was 63 years, with CAD occurring in more than 50% of the cases. A total of 93% had low C-peptide levels and 56% were anti-GAD antibody positive. In addition, 10 patients exhibited immunotherapy-induced thyroid abnormalities.[6]

Immunotherapy-induced thyroiditis is usually self-limited. Diagnosis is clinical, although sometimes, as in the case described, patients are usually asymptomatic, and it is the analytical data of thyroid hormones that alerts us about this complication. In the initial stages, thyroiditis is presented with analytical hyperthyroidism, so differential diagnosis must be established with GBS, which has also been described in patients on immunotherapy. The results of anti-TSI antibodies for the diagnosis of GBS usually take 2–4 weeks, so sometimes in the presence of hyperthyroidism without a clear diagnosis of thyroiditis, treatment can be started with antithyroid drugs, although in the absence of any diagnostic doubts between the 2 entities, the treatment of thyroiditis is usually symptomatic with anti-inflammatory drugs in the presence of anterior cervical pain or β-blockers if tachycardia or palpitations, with subsequent analytical follow-up based on disease progression. In the event of hypothyroidism, it is advisable to start hormone replacement therapy with levothyroxine 1.6–1.8 mcg/kg daily, performing hormone follow-ups and dose titration, if necessary, which in these cases usually requires higher doses.[3]

Mosaferi et al. compared the thyroid hormone replacement dose required to achieve euthyroid status in 118 patients with primary hypothyroidism vs 66 with hypothyroidism due to immunotherapy, 71.2% treated with monoclonal anti-PD-1, with TSH >4.7 mIU/L being considered hypothyroidism. They concluded that the primary hypothyroidism group required a mean dose of 1.25 (SD, 0.49) mcg/kg/day while those with immunotherapy-induced hypothyroidism required 1.45 (SD, 0.47) mcg/kg/day.[7]

Areas of uncertainty

One of the most controversial points is whether immunotherapy should be temporarily or permanently discontinued. According to what has been described in the available literature, in the case of DM when insulin therapy is started immediately, it would not be necessary to withdraw immunotherapy since the risk associated with the condition would be controlled with insulin.[8] In the case of thyroiditis, it is recommended to stop immunotherapy in grade 2–4 until the patient becomes asymptomatic and, then, restart treatment, if necessary, so the initial symptoms of thyroiditis can be treated with β-blockers. In the case of hypothyroidism, it would only be necessary to discontinue treatment in grade 3 and 4 until the patient becomes asymptomatic, even if hormonal control has not fully occurred.[9]

Glucocorticoids have proven ineffective in slowing disease progression. The risk of developing these conditions increases with prior immunotherapy administration or if they are concomitant therapies.[4] Furthermore, in cases which had previously developed other immunotherapy-related endocrine disorders, or if a predisposing HLA for DM is present. The pre-existence of T2DM does not increase the risk of developing this condition.

Clinical practice guidelines

Reviewing the available literature, there are some discrepancies in the management of these 2 types of adverse effects of immune checkpoint inhibitors.

According to the ASCO guidelines, in grade 1 thyroiditis, it is recommended to continue immunotherapy and prescribe β-blocker treatment if symptoms are present. In grade 2, it is considered to temporarily discontinue immunotherapy until clinical remission has been achieved, and in grade 3 and 4, immunotherapy should be discontinued until reaching clinical remission and hormonal normalization. It is recommended to start β-blockers if symptoms are present and persist for >6 weeks as well as in grade 3 or 4, antithyroid drugs should be recommended, with no specific initial dose. In the event of severe persistence, radioactive iodine and surgery may be considered.[10]

In the case of hypothyroidism, it is recommended to discontinue immunotherapy depending on the degree of severity of the condition. Regarding dose, it is advised to start levothyroxine at 1.6–1.8 mcg/kg/day in <70-year-old patients without comorbidities and start 25–50 mcg/day in >70-year-old patients with comorbidities and gradually titrate doses.[10]

For diabetes, it is recommended not to discontinue immunotherapy for grade 1 toxicity, but to suspend it for grades 2–4 until toxicity is controlled or returns to grade 1. However, maintaining immunotherapy at grade 2 is an option if deemed appropriate by the specialist. Insulin initiation is recommended at a total dose of 0.3–0.4 IU/kg/day, divided into basal and bolus therapy.[10]

According to SITC guidelines, for thyroiditis and hypothyroidism, as well as diabetes, it is recommended to replace hormonal deficiencies and resume immunotherapy as soon as possible, noting that suspension is often unnecessary. However, if diabetes presents as ketoacidosis, immunotherapy should be suspended until acute symptoms resolve. In cases of severe hyperglycemia or ketoacidosis, the patient should be hospitalized for appropriate diabetological education, and CGM should be initiated as soon as possible for outpatient management.[11]

In the case of thyroiditis, the recommendation is to use β-blockers for symptomatology, and in the case of patients with asthma or chronic obstructive pulmonary disease, cardioselective β-blockers (atenolol or metoprolol) are the best choice. For hypothyroidism, young patients without comorbidities are advised to start levothyroxine at 1.6 mcg/kg/day. For patients older than 65 years or with cardiac disease, a lower starting dose of 25–50 mcg/day is recommended.[11]

Conclusions and recommendations

In conclusion, immune checkpoint inhibitor-induced adverse effects are common and inherent to these drugs mechanism of action. Therefore, it is important to actively monitor patients on this therapy as adverse events can end up being potentially serious. Although they are more likely to occur due to combined therapies, they also occur with monotherapies.

The case report described in this article demonstrates the importance of early recognition of immunotherapy-related adverse effects, in addition to the complex early treatment until clinical stabilization has been achieved, especially in the presence of more than 1 endocrinological complication. Our main goal must be to stabilize the patient to continue curative cancer treatment as soon as possible and avoid its discontinuation.

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