

New onset autoimmune diabetes mellitus and hypothyroidism secondary to pembrolizumab in a patient with metastatic lung cancer

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Summary

Immunotherapy has become an important pillar for the management of advanced cancer. Immune-related adverse events including endocrinopathies have been well described with programmed cell death 1 inhibitors such as pembrolizumab. While thyroid dysfunction is the most common endocrinopathy associated with pembrolizumab, new-onset autoimmune diabetes mellitus (DM) is extremely rare. The authors report a case of pembrolizumab-induced primary hypothyroidism and type 1 diabetes mellitus presenting with diabetic ketoacidosis (DKA). A 59-year-old female patient was treated with pembrolizumab for a stage 4 lung adenocarcinoma. She presented to the emergency department with hyperglycaemia-related signs and symptoms, such as polyuria, polydipsia, weight loss, vomiting, asthenia and dehydration, 3 weeks after her first dose of pembrolizumab. Laboratory evaluation revealed hyperglycaemia, hyperketonaemia and high anion gap metabolic acidaemia consistent with DKA. After prompt and adequate treatment of DKA, she transitioned to s.c. basal-bolus insulin. The diagnose of autoimmune DM was established based on the undetectable C-peptide levels and seropositivity for antiglutamic acid decarboxylase antibodies. Additional hormonal parameters revealed overt hypothyroidism and levothyroxine therapy was initiated. This case highlights the importance of blood glucose and thyroid function monitoring as an integral part of cancer treatment protocols for pembrolizumab and other immune checkpoint inhibitors.

Learning points:

- Programmed cell death 1 (PD1) inhibitors such as pembrolizumab can cause endocrine immune-related adverse events (irAE), including thyroid dysfunction and type 1 diabetes mellitus (T1DM).
- Thyroid dysfunction is the most frequent endocrine irAE secondary to PD1 inhibitors.
- Autoimmune diabetes and possible resultant diabetic ketoacidosis are rare, but life-threatening adverse events associated with pembrolizumab.
- Pembrolizumab-induced T1DM often present with relatively low HbA1c levels, reflecting the fulminant onset of β -cell destruction.
- Patients treated with pembrolizumab and other immune checkpoints inhibitors should be monitored regularly for hyperglycaemia and thyroid dysfunction.



Background

Immunotherapy revolutionized cancer treatment and improved the outcomes of patients with advanced neoplasms (1). Immune checkpoint inhibitors (ICIs) act by either blocking cytotoxic T-lymphocyte antigen 4 (anti-CTLA4), programmed cell death protein 1 (PD-1) or its ligand (2, 3).

Pembrolizumab is a humanized IgG4 MAB targeting the PD1 receptor (1). It is currently approved for the treatment of metastatic non-small cell lung cancer (NSCLC) and several other cancer types, including malignant melanoma, small cell lung cancer, squamous cell carcinoma of the head and the neck, classical Hodgkin lymphoma, advanced urothelial carcinoma, among others (4).

In some neoplasms, the production of the PD-1 ligand is increased. These molecules bind to the PD-1 receptor in T cells and inhibit the immune response against tumour cells (5). Based on this mechanism, anti-PD1 and anti-programmed cell death ligand 1 (PD-L1) ICIs have been developed. These molecules block the PD-1 pathway and thereby restore T cell function and anti-tumor immune system response (6). Although, when the PD-1 pathway is blocked, not only T cells targeting cancer survive but also autoreactive T cells targeting the pancreatic islet cells survive, which can cause autoimmune type 1 diabetes mellitus (T1DM) (7). Endocrine immune-related adverse events have been described with ICIs, including thyroid dysfunction, hypophysitis, adrenal insufficiency and T1DM. Pembrolizumab induced-new-onset autoimmune diabetes mellitus (DM) is extremely rare, occurring in 0.4% of the patients (2).

Case presentation

We report a case of a 59-year-old female patient with a medical history of hypertension and acute ischemic stroke medicated with aspirin, simvastatin, perindopril and omeprazole. The patient had no personal history of thyroid disease or DM. The family history was negative for diabetes or autoimmune diseases. She was referred to the pneumology department for further investigation of a solid pulmonary nodule measuring 13 mm in the right superior lobe detected on chest CT 2 years before the event. An 18F-fluorodeoxyglucose PET-CT scan revealed increased uptake in the primary lung, without evidence of distant metastatic disease. A brain MRI did not reveal metastatic disease. The patient underwent right upper lobectomy and histology was compatible with a lung adenocarcinoma

EGFR+ with PD-L1 expression above 50%. The patient showed progressive disease, 4 months after surgery, with hepatic and cervical lymph node metastasis, and was proposed for erlotinib. After 14 months of treatment with erlotinib (18 cycles), she suffered from progressive disease with brain metastasis. The patient was discussed in a multidisciplinary meeting, and it was decided to switch therapy to pembrolizumab 2 mg/kg. Blood tests prior to pembrolizumab initiation revealed fasting normoglycemia (glucose 93 mg/dL) and normal thyroid function, with thyroid-stimulating hormone (TSH) of 3.26 μ IU/mL (reference range 0.27–4.20 μ IU/mL) and free Thyroxine (fT4) of 15.1 pmol/L (reference range 12–22 pmol/L). She presented to the emergency department 3 weeks after her first dose of pembrolizumab with symptoms of polyuria, polydipsia, weight loss of approximately 4 kg, vomiting and asthenia progressively worsening over 3 days. On physical examination, she was conscious, oriented and revealed dehydration. The patient was afebrile and normotensive with a pulse of 99 b.p.m, respiratory rate of 26 breaths per min and oxygen saturation of 97% on ambient air. Her BMI was 22.9 kg/m², and she did not show any signs of insulin resistance such as acanthosis nigricans.

Investigation

Laboratory analyses (Table 1) showed hyperglycaemia (554 mg/dL) associated with ketone (beta-hydroxybutyrate) level of 4 mmol/L (reference range <0.6 mmol/L). An arterial blood gas subsequently revealed high anion gap metabolic acidaemia: pH 7.31, pCO₂ 28 mmHg, HCO₃ 17.7 mmol/L, anion gap 18.9 mmol/L, lactate 1.5 mmol/L. The diagnosis of new-onset DM with diabetic ketoacidosis (DKA) was established and she was treated accordingly.

Additional tests were performed (Table 1) and demonstrated serum C-peptide below 0.2 ng/mL,

Table 1 Laboratory data at DKA diagnosis.

Investigation	Result	Reference range
Hemoglobin (g/dL)	10.1	12–15
White cell count ($\times 10^9$ /L)	4.4 $\times 10^9$ /L	4–10
Platelet count ($\times 10^9$ /L)	107	150–400
Creatinine (mg/dL)	1.09	0.50–0.90
Blood urea nitrogen (mg/dL)	31	17–49
Corrected sodium (mmol/L)	133	136–145
Potassium (mmol/L)	4.58	3.5–5.1
Phosphorus (mg/dL)	3.7	3–4.5
Serum C peptide (ng/mL)	<0.2	1.1–4.4
HbA1c (%)	5.6	<6.5
Total serum osmolality (mOsm/kg)	308	275–295
Lipase (U/L)	12	13–60



with a concomitant blood glucose of 191 mg/dL (normal range at our laboratory for serum C-peptide: 1.1–4.4 ng/dL) and HbA1c 5.6%. The antibodies associated with T1DM were positive for anti-glutamic acid decarboxylase (GAD) (48.9 U/mL, positive if ≥ 2 U/mL) and negative for islet cell, insulin and zinc transporter.

Additional hormonal parameters revealed primary hypothyroidism due to thyroiditis: TSH 40.9 μ IU/mL (reference range 0.27–4.20 μ IU/mL), fT4 5.57 pmol/L (reference range 12–22 pmol/L) with elevated thyroid peroxidase antibodies (ATPO 171 IU/mL, < 35 IU/mL). Adrenocorticotrophic hormone (14 pg/mL) and morning serum cortisol (8:00 h cortisol 36 μ g/dL) excluded adrenal insufficiency. The follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were within the normal reference values for the age and sex of the patient.

Abdominal CT did not reveal metastatic disease of the pancreas. She was not under treatment with glucocorticoids. No other DKA precipitating factors, besides pembrolizumab, were identified.

Treatment

The patient was treated according to the DKA protocol with i.v. isotonic saline fluid replacement, continuous insulin infusion for 8 h and was subsequently transitioned to a basal-bolus insulin regimen with insulin analogues after the resolution of DKA. Treatment with levothyroxine was also initiated.

Outcome and follow-up

After discharge, she was followed in endocrinology and pneumology outpatient clinics. On follow-up, she continued to require multiple daily insulin injections with insulin glargine (32 units once daily) and lispro (6 units with meals). Levothyroxine replacement was slowly titrated to 112 μ g, and euthyroidism was achieved 3 months after the diagnosis of hypothyroidism. After the event, she suffered from progressive systemic disease and her condition deteriorated significantly during the follow-up. She was discussed in a multidisciplinary meeting, and it was decided to not restart pembrolizumab due to a significant decline in performance status. The patient's relatives refused further aggressive treatment and opted for the best supportive care. The patient died 6 months after the event due to complications of her metastatic NSCLC and acute ischemic stroke.

Discussion

Immunotherapy revolutionized oncology treatment for many advanced neoplasms since 2011 and their use is rapidly increasing (2). Consequently, the number of patients experiencing irAE related to ICIs as pembrolizumab will expectedly increase (2).

Pembrolizumab was approved by the Food and Drug Administration in 2015 for metastatic NSCLC (1). Despite the remarkable survival benefits of pembrolizumab in patients with NSCLC, it can be associated with serious irAE due to excessive immune system activation (6, 8). For unknown reasons, the endocrine system is particularly susceptible to immune-mediated damage by ICIs (5).

Pembrolizumab binds to the PD-1 receptor on T cells and blocks its interaction with PD-L1 presented on the surface of the tumour cells, restoring the immune system response against cancer cells (6).

Barroso-Sousa *et al.* reported a systematic review and meta-analysis evaluation of the endocrine irAE in 38 clinical trials comprising 7551 patients with a diagnosis of advanced solid tumours under treatment with ICI. Thyroid dysfunction was the most common endocrine irAE in patients treated with PD-1 inhibitors, while hypophysitis was the most frequent endocrine dysfunction with ipilimumab (anti-CTLA4 antibody). Primary adrenal insufficiency and T1DM were rare adverse events with reported incidences of 0.7 and 0.2%, respectively (9). Thyroid dysfunction usually presents as silent inflammatory thyroiditis that develops within weeks to months after immunotherapy initiation (1). Graves' disease and Euthyroid Graves' disease secondary to ICI were also, rarely, reported. Previous studies revealed a higher incidence of anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies in patients with thyroid dysfunction associated with ICI, suggesting a possible connection of immunologic pathways with thyroid dysfunction induced by ICI (8).

The mechanism for which pembrolizumab induced T1DM is not fully understood. Although, some authors proposed that insulin deficiency results from inappropriate activation of autoreactive T cells targeting pancreatic β islet cells when the PD-1 pathway becomes inhibited (7). In our case, the presence of anti-GAD antibodies favours an immune-mediated subtype of T1DM. The predisposing risk factors for ICI-induced diabetes have not yet been fully recognized. Nevertheless, there was a preponderance of high-risk HLA haplotypes (e.g. HLA-DR4) in patients with ICI-induced T1DM, suggesting a genetic predisposition (2, 8).



Clotman *et al.* reported a systematic review evaluating 42 cases of T1DM induced by PD-1 inhibitors. The median age of diagnosis was 63 years and 30 patients presented with DKA at diagnosis. Most of the cases were associated with nivolumab ($n = 21$), while 12 were associated with pembrolizumab monotherapy. T1DM was diagnosed following a median of 6 weeks (range 1–52 weeks) after the initiation of the PD-1 inhibitor. Ninety-three percent had low c-peptide and 56% had positive anti-GAD antibodies. Ten patients had concurrent thyroid dysfunction induced by PD-1 inhibitors. Most patients had to restart immunotherapy without an impact on glucose control and remained with stable insulin requirements (7).

The onset of β cell destruction is often fulminant suggested by relatively low HbA1c levels, while C-peptide levels are usually low or undetectable at diagnosis (7). The majority of patients presented with fulminant diabetes, and DKA is reported in about 57% of the patients (2). Our patient presented a low HbA1c level (HbA1c 5.6%) with suppressed C-peptide (below 0.2 ng/mL, with a concomitant blood glucose of 191 mg/dL), reflecting the acute onset of ICI induced-T1DM. Currently, the standard treatment of ICI-induced diabetes is insulinotherapy (2).

According to French Endocrine Society Guidelines regarding endocrine side effects of immunotherapy, patients under treatment with anti-PD1 and anti-PD-L1 should be performed before each course of therapy blood tests evaluating fasting glucose, thyroid function (TSH and fT4), serum sodium, 8:00 h cortisol, FSH, LH and testosterone in males and oestradiol in females with irregular cycles at each appointment during the first 6 months and at every second appointment over the following 6 months or in case of symptoms (2). Physicians should educate the patients on recognizing symptoms suggestive of endocrine irAE (1, 2). Interestingly, in recent years the occurrence of endocrine and other irAE has been associated with anti-tumour efficacy of ICIs and better outcomes, possibly due to a more competent immune system, or cross-reactivity between tumour and host tissue (2). Although, these results could also be biased due to the longer exposure in patients that responded to Immunotherapy and further research is necessary (2). The development of thyroid dysfunction or T1DM is not a contraindication for immunotherapy. When a patient presents with severe hypothyroidism, thyroid storm or DKA, ICI can be postponed and restarted when the patient is stabilized (2).

In conclusion, our patient had two endocrine irAEs associated with pembrolizumab treatment, namely T1DM presented with DKA and primary hypothyroidism. Checkpoint inhibitors-induced autoimmune T1DM

is a rare but potentially life-threatening complication, as DKA, is often the first presentation. As symptoms of endocrinopathies may be non-specific, a high index of suspicion and multidisciplinary team approach with monitoring protocols are the keys to prompt diagnosis and rapid institution of treatment for these immune-related endocrinopathies (10).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of their clinical details was obtained from a relative of the patient after patient's death.

Author contribution statement

C C drafted the manuscript. E S, A C V and C S reviewed and edited the manuscript prior to submission. C C, E S and A C V were the physicians who contributed to the care of the patient. S D also performed final editing of the manuscript and gave the approval to submit the manuscript for publication.

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