Anti-PD-1 immune checkpoint inhibitor inducing endocrine toxicity in a patient with advanced lung cancer: A case report and literature review

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Abstract. The anti-programmed cell death protein 1 (anti-PD-1) antibody is a breakthrough immune checkpoint inhibitor that modulates T-cell function. However, it may result in multiple immune-related adverse events (irAEs), such as endocrine toxicity. The present case report describes a 59-year-old female patient with advanced non-small cell lung cancer with a tumor proportion score of 50% for programmed death ligand 1. The patient developed dry skin, dizziness and fatigue after receiving the third infusion of the anti-PD-1 antibody pembrolizumab. Based on several clinical indicators, including low serum free T3 and free T4 titers, an elevated thyroid-stimulating hormone level and a high titer of thyroid peroxidase autoantibody, the patient was diagnosed with immune-induced autoimmune thyroiditis. The patient received continuous thyroxine replacement therapy until her thyroid function returned to normal. After the fifth infusion of pembrolizumab, the patient exhibited hyperglycemia, high serum ketone levels and low arterial blood pH, thus meeting the criteria for immune-induced autoimmune diabetes and diabetic ketoacidosis. As a result, the immunotherapy was discontinued and the patient was diagnosed with insulin-dependent diabetes mellitus. Following anti-PD-1 medication, the patient experienced autoimmune thyroid damage and autoimmune diabetes. Therefore, clinicians should regularly monitor patients undergoing immunotherapy and pay close attention to the characteristics irAEs. Patients with underlying thyroiditis should be carefully monitored due to this being a risk factor, and for patients with thyroiditis care should be taken when deciding on whether they should be treated with immunotherapy. The article also discusses the features and general mechanisms of immune-related endocrine toxicity.

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Introduction

Immunotherapy has emerged as a powerful technique for tumor treatment over the past decade. The most striking research is on the programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) signaling pathway, which has a negative regulatory role in immune response (1,2). Inhibition of the PD-1/PD-L1 signaling pathway may reactivate the recognition and cytotoxicity of the immune system to tumor cells, significantly improving the prognosis for numerous advanced cancers, such as melanoma and non-small cell lung cancer (NSCLC), as well as cervical, kidney and colorectal cancers (3,4).

For the treatment of several malignancies, the Food and Drug Administration has authorized the use of PD-1/PD-L1 inhibitors, such as nivolumab, pembrolizumab, durvalumab, atezolizumab and avelumab (5). However, immune checkpoint inhibitor (ICI) therapy frequently comes with immune-related adverse events (irAEs) (6). These effects mainly depend on the diverse tumor and ICI types, distinct from those observed in traditional chemotherapy (7). Some of the irAEs are organ specific events, mainly involving the thyroid, lung, colon, liver and pituitary gland (8). In addition, ICIs can induce some rare and fatal events, such as myocarditis and neurotoxicity (9).

PD-1/PD-L1 inhibitors may cause unpredictable endocrine toxicity and frequently involve the thyroid, pituitary gland and pancreas (10). Thyroid dysfunction, autoimmune diabetes, pituitary inflammation and primary adrenal insufficiency are the main irAEs of the endocrine system (11). These complications may markedly affect the patient's health and quality of life (12).

The present study reported on a patient with advanced NSCLC treated with immunotherapy, who acquired autoimmune hypothyroidism, autoimmune diabetes and diabetic ketoacidosis (DKA). The treatment procedure for the case was also discussed, together with a literature review.

Case report

A 59-year-old female patient was diagnosed with advanced NSCLC in May 2020 by pathological biopsy in Tianjin First Central Hospital (Tianjin, China). The patient had no prior history of diabetes. However, the patient took statins for elevated blood lipids, which may have influenced her blood

glucose levels (13). Therefore, the patient's blood glucose was monitored and the level remained normal prior to starting immunotherapy. In addition, the patient had Hashimoto's disease, with a high thyroid peroxidase autoantibody (TPOAb) titer of 35.2 μg/l (Table I). The patient did not take any drugs to treat it, as she had no related symptoms.

An immunotherapy plus chemotherapy regimen was administered according to the Chinese Society of Clinical Oncology guidelines for NSCLC (2020 version) (14). The patient received five courses of carboplatin combined with pemetrexed due to wild-type EGFR. The patient was monitored regularly and no noticeable abnormality was found during chemotherapy. Further periodic laboratory examinations were performed to examine fasting blood glucose (FBG) levels and thyroid function, and the results remained normal. The degree of PD-L1 expression in tumor samples was assessed after chemotherapy and roughly 50% of the tumor cells stained positively for PD-L1. Therefore, the patient received an anti-PD-1 antibody, pembrolizumab, 2 mg/kg every 3 weeks (15).

The patient developed rough skin, dizziness, fatigue and dropsy following the second pembrolizumab injection. These symptoms gradually worsened after the third infusion. As presented in Table I, laboratory tests revealed decreased free T3 (FT3) and free T4 (FT4) levels and elevated titers of thyroid-stimulating hormone (TSH) and particularly TPOAb, with the titer reaching 950.67 μg/l. Other indicators, such as FBG and thyroglobulin antibody (TgAb), were within the normal ranges.

The patient was clinically diagnosed with pembrolizumab-induced thyroid damage (16). The patient felt better following continuous thyroxine replacement therapy and thyroid hormone levels returned to normal. After treatment for six weeks, the patient's thyroid hormone levels returned to normal following replacement therapy with 75 μg of levothyroxine per day. Considering the patient's strong desire for immunotherapy and the excellent recovery of thyroid function, we decided to proceed with the remaining courses. Her blood glucose level has remained within normal limits.

At two weeks after the fifth infusion of pembrolizumab, the patient presented with polydipsia, polyuria, general fatigue, nausea, vomiting and confusion, so she was admitted to the emergency department. The patient exhibited no limb twitching, incontinence or neurological system abnormalities. Table I indicated that the patient's random blood glucose level was elevated to 29.9 mmol/l, and there was a high ketone level in the urine, with serum ketone reaching 4.9 mmol/l.

The levels of insulin secretion were all lower than the detection limits, including fasting C-peptide and C-peptide, 2 h after a meal. The patient's arterial blood gas analysis indicated an arterial blood pH of 6.8, the base excess in the extracellular fluid compartment (BEecf) was as low as -27.6 mmol/l and there were high levels of anion gap (AG), which suggested metabolic acidosis. Physical examination revealed that the patient had a body temperature of 36.3˚C, a blood pressure of 102/74 mmHg, a pulse of 112 bpm and a body mass index (BMI) of 21.5 kg/m^2. Other results for the neurological system and other systems were insignificant.

Therefore, the patient's laboratory findings (including hyperglycemia, high serum ketone and low arterial blood pH) met the criteria for a diagnosis of DKA (17). After a comprehensive discussion and literature review, it was determined that the patient had pembrolizumab-induced autoimmune diabetes and DKA, which resulted in immunotherapy termination. The patient was given continuous subcutaneous insulin infusion (CSII) to correct the acidosis. The patient's blood glucose level returned to normal after CSII treatment and the symptoms of discomfort vanished. Considering the patient's poor pancreatic islet function, the regimen was adjusted to daily insulin injections after the patient was discharged from the hospital. The patient is currently receiving palliative care for NSCLC as an insulin-dependent patient with well-controlled diabetes.

Discussion

Previous studies have focused mainly on organ-specific irAEs, in which the effects were mild and reversible and mostly associated with the skin and gastrointestinal tract, such as pruritus, rash and diarrhea, as also observed in the present case (18). Limited information is available regarding the connection between anti-PD-1/PD-L1 therapy and severe endocrine toxicity (12). Immune-related endocrinopathies, including hypophysitis and hypothyroidism, are difficult to diagnose because of their nonspecific and rare symptoms (17).

The most striking findings of the present case report were the markedly short time over which destructive thyroiditis was induced and the pancreatic damage following the infusion of the anti-PD-1 antibody pembrolizumab. The patient's blood glucose and thyroid function were routinely monitored under the European Society for Medical Oncology (ESMO) guidelines, according to which routine laboratory tests are required every two courses or at least once a month (19). As revealed in Table I, the serum level of the specific indicator known as TPOAb for the diagnosis of Hashimoto's disease was outside the normal range and consistent with the patient's previous medical history. However, the situation changed after the patient completed the third injection.

Considering the atypical symptoms and aberrant thyroid function, it was concluded that the patient's destructive thyroiditis was aggravated by the administration of pembrolizumab. Similarly, Nogueira *et al* (20) retrospectively analyzed 179 patients with advanced cancers receiving different ICIs and determined that preexisting thyroid dysfunction was a significant risk factor for predicting thyroid toxicity. Furthermore, Xie *et al* (21) revealed that patients who received PD-1/PD-L1 inhibitors were more likely to have endocrine dysfunction than those receiving cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitors and chemotherapy, which may explain the severe thyroid toxicity in the present case. As a result, patients with abnormal thyroid function at baseline should be carefully assessed when undergoing immunotherapy.

The blood glucose level remained normal even after the third pembrolizumab injection. However, two weeks after the five courses of immunotherapy, a series of clinical symptoms and blood test results proved that the patient had DKA and her pancreatic function had been irreparably damaged. Due to this severe complication, it was decided to re-examine certain rare but fatal irAEs (22). Lack of attention to such irAEs by doctors and patients is one issue that may cause a short delay in the precise treatment. Marchand *et al* (23) concluded that autoimmune diabetes was not related to type 1 diabetes (T1D)-related

Table I. Clinical and biochemical parameters of the patient.

Parameter	Reference range	After five courses of carboplatin combined with pemetrexed chemotherapy	After the third infusion of pembrolizumab, before levothyroxine replacement therapy	After the fifth infusion of pembrolizumab, with 75 μg per day of levothyroxine replacement therapy
BMI, kg/m^2	18.5-23.9	21.5	22.1	21.8
Fasting blood glucose, mmol/l	3.9-6.1	4.4	5.2	ND
Random blood glucose, mmol/l	≤11.1	ND	ND	29.9
2-hour postprandial blood glucose, mmol/l	3.9-7.8	6.8	7.6	ND
HbA1c, %	4.0-6.0	5.3	5.6	8.5
Thyroid-stimulating hormone, mIU/l	0.27-4.2	2.5	>100	4.0
FT3, pmol/l	3.1-6.8	3.7	1.18	3.4
FT4, pmol/l	12-22	13.6	2.7	13.2
TPOAb, μg/l	0-9	35.2	950.67	678.5
TgAb, μg/l	1.15-130.7	15.6	70.05	62.1
Blood ketones, mmol/l	0.03-0.30	ND	ND	4.9
Arterial blood pH	7.35-7.45	ND	ND	6.8
BEecf, mmol/l	-3-+3	ND	ND	-27.6
C-peptide (fasting), ng/ml	1.1-4.4	ND	ND	<0.02
C-peptide (2 h after meal), ng/ml	ND	ND	ND	<0.02
Islet-related autoantibodies	ND	ND	ND	
ICA	ND	ND	ND	Negative
IAA	ND	ND	ND	Weakly positive
GAD antibody	ND	ND	ND	Negative

BMI, body mass index; HbA1c, glycosylated hemoglobin; FT3, free T3; FT4, free T4; TPOAb, thyroid peroxidase autoantibody; TgAb, thyroglobulin antibody; ICA, islet cell antibodies; IAA, insulin autoantibodies; GAD, glutamic acid decarboxylase; BEecf, base excess in the extracellular fluid compartment; NA, not available.

autoantibodies, which meant that there is no biomarker for predicting immunotherapy-induced diabetes. The median time from the initiation of immunotherapy to diabetes onset was 4 months. However, this is not able to represent the general pattern of diabetes onset, since only six participants were included in that study. Therefore, future investigations are necessary to develop preventive strategies and identify patients with increased vulnerability to acquire autoimmune diabetes.

The toxicity profiles of ICIs are displayed in distinctive and different ways alongside organ-system events as an increasing number of patients receive immunotherapy, such as immune-related pneumonia, hepatitis, colitis, endocrine system diseases and skin inflammation (3,8). Despite their rarity, endocrine toxicities are a common source of acute and persistent illnesses (24). The present study discussed the general characteristics and mechanisms of endocrine toxicity during immunotherapy.

PD-L1 is highly expressed in normal thyroid tissue (25). Targeting the PD-1/PD-L1 signaling pathway may induce autoimmune thyroid damage (26). An estimated 10-20% of cancer patients receiving anti-PD-1/PD-L1 antibodies may develop thyroid problems such as hyperthyroidism, thyroiditis and hypothyroidism (27). Certain studies indicated that patients with baseline TPOAb and TgAb positivities were substantially more likely to acquire thyroid disorders than patients without those antibodies (28,29). Individuals with underlying thyroiditis should be treated with particular caution when receiving immunotherapy.

Thyroid dysfunction primarily manifests as hypothyroidism. The median time to onset of thyroid dysfunction is roughly 6 weeks after immunotherapy initiation, which was also observed in the patient of the present study. Thyroid dysfunction may occur at any point in time while patients are using ICIs (30). Thyroid biopsies have been employed for individuals with immune-related thyroiditis in order to investigate the pathogenic nature of elevated lymphocytic infiltration in thyroid tissue (31). There was no evidence that patients who had a history of autoimmune thyroid dysfunction experience more prominent thyroid toxicity when treated with anti-PD-1/PD-L1 therapy.

In general, those patients with immune-related hypothyroidism who exhibit fatigue, depression and weight gain may have decreased FT4 and FT3 levels, but an elevated concentration of TSH. Thyroid hormone replacement should be given if the TSH levels are markedly raised by >10 mIU/l (10).

Immunotherapy-related thyrotoxicosis is characterized by low TSH and increased FT4 or total T3 levels, the symptoms of which may be slight or moderate (26,27). Approximately 70% of patients with thyroiditis are susceptible to hypothyroidism after 6 weeks. Thus, such individuals should receive regular monitoring (32). A study of 151 patients with immune-related thyroid disorders indicated that the transition time from thyrotoxicosis to hypothyroidism was not impacted by high doses of glucocorticoids (33). Treatment for thyroiditis-associated thyrotoxicosis generally consists of beta blockers for symptomatic relief (34). Therefore, increasing the awareness of autoimmune thyroid disorders among oncologists and endocrinologists may improve the safety and efficacy of immunotherapy in high-risk patients.

In the present study, the patient had normal thyroid hormone levels prior to immunotherapy, but an elevated TPOAb level was present, suggesting that autoimmune thyroid disease may not be excluded. After three courses of pembrolizumab, the patient developed clinical symptoms, such as fatigue, rough skin and edema, and the TPOAb titer was significantly higher than previously, suggesting the presence of immune-mediated hypothyroidism. The patient's thyroid function recovered well after treatment with levothyroxine. Several studies also suggested that thyroid function may be restored after immunotherapy was completed; however, there was no requirement for additional levothyroxine replacement therapy (10,26). Immunotherapy was continuously administered to the patient until DKA occurred as a serious complication.

Numerous studies have indicated a substantial correlation between ICIs and diabetes mellitus (DM) (35). ICI-DM has been functionally defined as severe and persistent insulin deficiency in patients following immunotherapy. T1D caused by PD-1/PD-L1 inhibitors is rare, with reported prevalence rates ranging from 0.2 to 0.9% (36). Approximately 50% of patients with ICI-DM have detectable islet autoantibodies on presentation (37). Patients with islet autoantibodies receiving immunotherapy may develop T1DM more rapidly than patients without those antibodies (38).

In 2015, Martin-Liberal *et al* (39) first reported that a 54-year-old female patient with melanoma developed autoimmune diabetes after being treated with PD-1/PD-L1 inhibitors. The first case of diabetes after ICI treatment in China was reported in 2018 (40). The PubMed database was searched between 2012 and 2022 with the following keywords 'nivolumab', 'pembrolizumab', 'atezolizumab', 'diabetic ketoacidosis', and 'non-small cell lung cancer'. Selection criteria included: i) the application of the above drugs for NSCLC; ii) clear reported DM events; and iii) English literature. Moreover, the cancer cases treated with the CTLA4 inhibitor ipilimumab or other ICIs were excluded. Finally, the previous cases reported in the literature are summarized in Table II (40-50). From the previous cases, the characteristics of ICI-DM may be defined as a quick rise in blood glucose and a swift fall in the endogenous insulin concentration. T1DM was typically caused by PD-1/PD-L1 inhibitors a small number of weeks or months following treatment. Patients may develop DKA with rapid onset and they may have undetectable insulin C-peptide levels (36). Due to the rapid onset of DM, patients with ICI-DM may test positive for diabetes autoantibodies. Of note, this differs from conventional T1DM (51).

The exact mechanism of the occurrence of ICI-DM remains to be fully elucidated. It may be related to the suppression of PD-1/PD-L1-mediated negative immunological signals, which in turn causes the attack of autoreactive lymphocytes, and $CD8^+$ T cells may be crucial in mediating ICI-DM (4,10). Therefore, blood glucose and glycated hemoglobin should be periodically checked in patients receiving immunotherapy. In addition, blood glucose testing should be performed for patients with gastrointestinal symptoms (including nausea and vomiting), as there is a possibility of DKA.

The patient of the present study exhibited elevated blood glucose levels 12 weeks after the beginning of immunotherapy, along with polydipsia, polyuria and general fatigue, and later presented with nausea and vomiting. It may be speculated that a specific pattern of T1DM caused by immunotherapy may induce autoimmune diabetes and even DKA, and that pembrolizumab therapy for patients with T1DM should be combined with insulin therapy. For patients with grade 3 or 4 hyperglycemia (FBG ≥13.9 mmol/l) or DKA, pembrolizumab should be suspended until the condition is under control. Patients should be followed up continuously until their blood glucose level is stable to determine whether pancreatic islet function and blood glucose levels have been restored and whether insulin maintenance treatment is still required after cessation of PD-1/PD-L1 immunotherapy.

Hypophysitis occurs in 0.5-1% of individuals with advanced cancer who receive immunological monotherapy. It was speculated that hypophysitis may be related to lymphocyte infiltration into the pituitary and the presence of circulating antipituitary antibodies (52).

A retrospective study indicated that most individuals with pituitary dysfunction displayed typical symptoms and the median time to presentation was ~26 weeks after the start of ICI monotherapy (53). The symptoms included headache, nausea, vomiting, diplopia, visual field deficits, or, more commonly, secondary adrenal insufficiency, while severe cases presented with hypotension or adrenal crisis (54). Low morning cortisol (<5 mcg/dl) and acetylecholin (ACTH) levels may indicate secondary adrenal insufficiency, while low TSH and FT4 levels are indicators for diagnosing secondary hypothyroidism. Furthermore, low sex hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are signs of secondary hypogonadism. In addition, patients with adrenal insufficiency should receive replacement therapy, if necessary, which includes glucocorticoids, thyroid hormones, testosterone and estrogen (23).

In the case of the present study, pituitary function was evaluated at the onset of hypothyroidism, diabetes and DKA, respectively. When detecting pituitary hormones (ACTH, growth hormone, FSH, LH and prolactin), the circadian rhythm of blood cortisol secretion at 08:00, 16:00, and 24:00 h; 24-hour urinary cortisol; blood electrolytes (sodium, potassium, chlorine); and sex hormone levels, no significant abnormality was determined (results not shown), indicating that the patient's pituitary function was not affected and that there was no immune-related hypophysitis. However, following the third infusion of pembrolizumab, laboratory tests revealed elevated TSH and TPOAb levels and decreased FT3 and FT4

Table II. Anti- PD-1/PD-L1 inhibitors inducing DKA in NSCLC.

Author, year	Other medical history	Agent and dose	Occurrence time	Peptide, ng/ml	HbA1c, %	Blood glucose, mg/dl	Relative autoantibody	Other adverse effect	(Ref.)
Ishi, *et al*, 2021 May	T2DM	Nivolumab, chemotherapy, atezolizumab	After the 1st cycle	<0.1	9.3	788	Anti-GAD (-), IA-2 (-), IAA (-)	None	(49)
Godwin, *et al*, 2017 May	None	Chemoradiation, nivolumab	After the 2nd cycle	<0.1	7.1	377	Anti-GAD (+), IA-2 (+), IAA (+)	None	(41)
Lee, *et al*, 2018 Apr	Hypertension, hypercholesterolemia, COPD, T2DM	Chemoradiation, nivolumab	After the 2nd cycle	<0.1	7.6	515	Anti-GAD (+)	None	(42)
Lupi, *et al*, 2019 Oct	T1DM	Atezolizumab	After the 4th cycle	NA	NA	180	Anti-pituitary (+)	Hyponatremia, hyperkalemia	(43)
Sothornwit, *et al*, 2019 Jun	None	Atezolizumab, paclitaxel and carboplatin	24 weeks after the 1st cycle	<0.1	7.9	332	Anti-GAD (+)	Neuralgia, transaminitis	(44)
Patel, *et al*, 2019 Dec	None	Durvalumab	3 months after the 1st cycle	<0.1	7.8	362	Anti-GAD (+)	Hypothyroidism	(45)
Skorpen, *et al*, 2019 Feb	None	Pembrolizumab	16 days after the 2nd cycle	<0.1	8.4	NA	Anti-GAD (-), IA-2 (-), IAA (-)	None	(46)
Leonardi, *et al*, 2017 Jul	None	Pembrolizumab	After the 3rd cycle	0.3	7.6	636	Anti-GAD65 (+)	None	(47)
Li, *et al*, 2018 Nov	None	Pembrolizumab	One week after the 3rd cycle	0.51	8	534	Anti-GAD (-), IA-2 (-), IAA (-)	None	(40)
Kusuki, *et al*, 2020 Apr	Colon cancer	Carboplatin and pemetrexed, pembrolizumab	After the 5th cycle	0.39	8.1	488	NA	NA	(48)
Alrifai, *et al*, 2019 Nov	T2DM	Carboplatin and pemetrexed, pembrolizumab	20 days after the 4th cycle	<0.1	9.2	907	Anti-GAD (+)	None	(50)

PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; DKA, diabetic ketoacidosis; NSCLC, non-small cell lung cancer; HbA1c, glycosylated hemoglobin; COPD, chronic obstructive pulmonary disease; GAD, glutamic acid decarboxylase; IA-2, tyrosine phosphatase-related islet antigen 2; IAA, insulin antibodies; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; NA, not available.

levels, suggesting that the patient had hypothyroidism, which was likely to be caused by immune-related thyroiditis. The patient's TSH and thyroid hormone levels returned to normal after levothyroxine supplementation.

In conclusion, immunotherapy has provided a new direction for tumor therapy (5). Thousands of patients with advanced cancer have benefited from ICIs (7). However, immunotherapy incurs multiple side effects (particularly endocrine toxicities), which lower immunological effectiveness and even endanger patients' lives (10). Therefore, it is crucial to monitor immunotherapy patients for blood glucose, HbA1c, thyroid function and pituitary function. Furthermore, clinicians should collaborate closely with endocrinologists to manage immune-related endocrinopathies for oncological patients and to be aware of irAE characteristics during and long after administering anti-PD1/PD-L1 antibodies. Clinicians should also instruct patients on how to recognize potential irAE symptoms.

Further studies are required to clarify the pathogenesis of immune-related endocrine diseases and offer new prospects for investigating potential therapies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SB and XJ were responsible for data collection and analysis, as well as manuscript writing and revision. All authors read and approved the final manuscript. SB and XJ confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Tianjin First Center Hospital (Tianjin, China; approval no. E2020N229KY).

Patient consent for publication

Written informed consent was obtained from the patient for the case report and the publication of her clinical information.

Competing interests

The authors declare that they have no competing interests.

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