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Diabetes mellitus secondary to treatment with immune checkpoint inhibitors

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ABSTRACT

Cancer immunotherapy has been one of the highlights in the advancement of cancer care. Certain immune checkpoint inhibitors bind to PD-1 on T cells and mediate an antitumour immune response. Given that immune checkpoint inhibitors are becoming part of standard care, a new class of adverse events—immune-related adverse events—has emerged. Among them is endocrine toxicity, most commonly targeting the thyroid, pituitary, or adrenal glands. New-onset diabetes mellitus has been reported in fewer than 1% of patients. We present a patient with type 1 diabetes mellitus secondary to immunotherapy, together with an overview of the associated literature. Patients who develop type 1 diabetes mellitus experience a rapid course, and diabetic ketoacidosis is commonly the presenting symptom. Insulin is currently the treatment of choice; oral antidiabetics or corticosteroids do not assist in management. Several predictive factors are under investigation, but physician awareness and prompt management are key to a positive outcome.

Key Words   Immune checkpoint inhibitors, diabetes mellitus, immunotherapy, immune-related adverse events, irAEs, nivolumab

INTRODUCTION

In the past few years, immunotherapy has been integrated as part of routine cancer care. Agents targeting immune checkpoints have proven to be effective against several types of cancer such as non-small-cell lung carcinoma and melanoma[1–3], and they continue to make headway in the treatment of other types of cancer as well[4,5].

The immune response is regulated by the balance between inhibitory and stimulatory signals. Immune checkpoints are regulatory molecules that modulate T cell stimulation or inhibition, thereby preventing inadequate responses and promoting self-tolerance. One of the inhibitory pathways is the PD-1 pathway. The PD-1 protein is expressed on T cells in peripheral tissues, and when it binds to its ligands PD-L1 and PD-L2, it inhibits T cell proliferation[6]. The PD-1 pathway is exploited in the tumour microenvironment and promotes tumour immune evasion. Immune checkpoint inhibitors such as nivolumab and pembrolizumab bind to the PD-1 receptor, inhibiting the protein's interaction with its ligands, augmenting local immunity.

The encouraging effect of the immune checkpoint inhibitors on overall survival and progression-free survival was also accompanied by a toxicity profile that is better tolerated than that for conventional chemotherapy. However, T cell reactivation can also affect normal cells. Several immune-related adverse events have been described. Those events most commonly affect the skin, respiratory, gastrointestinal, and endocrine systems. New-onset type 1 diabetes mellitus (T1DM) has been reported in some patients after administration of immunotherapy. It usually presents with diabetic ketoacidosis and follows a rapid course. Awareness and prompt management are therefore key.

CASE DESCRIPTION

We present the case of a 71-year-old patient who was diagnosed with non-small-cell lung carcinoma. (The patient's written informed consent was obtained before submission.)

Initial staging with combined positron-emission tomography–computed tomography and magnetic resonance imaging revealed advanced disease with bilateral lung involvement, nodal spread, and metastatic bone disease. The patient's medical history was significant for tobacco use (80 pack–years). The patient was initially treated with chemotherapy (carboplatin–pemetrexed, docetaxel), but 1 year later, because of disease progression with asymptomatic brain metastasis, treatment with nivolumab 3 mg/kg was initiated.

After 10 months of treatment with nivolumab, the patient was hospitalized because of generalized weakness, polyuria, and polydipsia. At the time of admission, his blood glucose was 471 mg/dL (26 mmol/L), with no keto-acidosis. No prior personal or family history of diabetes mellitus was noted. He had no fever or symptoms suggesting infection. His pancreatic enzymes and thyroid and cholesterol studies were within the normal range. Findings on computed tomography imaging of the abdomen were not clinically significant. His serum HbA1C was 7.8%, and C-peptide levels were below 0.1 ng/mL.

The patient was initially treated with intravenous fluids and continuous insulin infusion. Upon further testing, he was not found to have high serum anti–glutamic acid decarboxylase antibodies or anti–islet cell antibodies. The diagnosis of nivolumab-associated T1DM was made (Table I).

When glucose levels were satisfactorily controlled 3 weeks later, the patient resumed treatment with nivolumab. He received 9 more months of treatment with nivolumab and remained insulin-dependent until his death from complications of his disease.

DISCUSSION

Checkpoint inhibitors have established effectiveness against a variety of cancers, but can also trigger immune-related adverse effects. Autoimmunity associated with PD-1 blockade was established in PD-1 knockout mice long before its application as part of routine cancer care[7,8]. Blockade of PD-1 and PD-L1 has also been shown to precipitate auto-immune diabetes mellitus in non-obese diabetic mice[9].

Immune-related adverse events are well recognized, present acutely, and can be life-threatening. Endocrinopathies most commonly manifest as thyroiditis, hypophysitis, adrenalitis, and occasionally, as diabetes mellitus. In a systematic review and meta-analysis that included 7551 patients, diabetes mellitus was reported in 0.2% of patients treated with checkpoint inhibitors[10]. Currently, more than 20 isolated reports of checkpoint inhibitor–induced diabetes mellitus can be found in the literature (Table II). Even though concrete associations cannot be made, certain similarities in the characteristics of those cases can be highlighted in terms of predicting their occurrence and managing them effectively.

The patients typically follow a fulminant course, with diabetic ketoacidosis[11–14,16–18,20,22,24,26,27] and rapid beta-cell destruction. The inability to produce endogenous insulin is documented early in the diagnosis by a steep decline in C-peptide levels[11,12,14,16–18,20–22,26,27]. Time of presentation is inconsistent; in several cases, however, diabetes mellitus occurred within the first 2 months after initiation of treatment with anti–PD-1 therapy[11–14,20–22,24,27]. Of great interest is the fact that many patients experienced more than 1 immune-related adverse event during anti–PD-1 treatment, with autoimmune thyroiditis being most commonly reported[11,12,14–17,20,22,24]. That observation is highly suggestive of a heightened vulnerability in autoimmunity for this population.

In the general population, T1DM is commonly, but not always, attributed to increased genetic risk and the presence of anti–glutamic acid decarboxylase antibodies, anti–islet cell antibodies, insulin antibodies, or insulinoma-associated 2 antibodies[28]. Accordingly, in cases of T1DM precipitated by immunotherapy, several patients were found to have high-risk human leucocyte antigen genotypes[12–14,16,19], and approximately 50% were found to be positive for relevant antibodies, with anti–glutamic acid decarboxylase antibodies being predominant[12–15,17,20–22,24,27]. Serum lipase[11,18,25], serum amylase, and elastase I[26] have been investigated as possible markers indicative of pancreatic inflammation.

Glucose control is universally achieved with insulin, and long-term exogenous insulin-dependence is inevitable even after discontinuation of treatment. It seems that diabetes mellitus results in complete beta-cell destruction and is therefore not reversible. Only a single case report mentioned reversal of insulin-dependence, but that patient had documented residual beta-cell function[15]. In another patient (who was treated with corticosteroids), prednisone did not contribute to glycemic control[21].

SUMMARY

Diabetes mellitus secondary to treatment with checkpoint inhibitors is a new entity. Given the rapid course of the condition's development, it is suggested that glucose levels be regularly monitored. The exact pathophysiologic mechanism and predictive biomarkers have not yet been established. The result is permanent insulin-dependence and, in a departure from treatment for other immune-related adverse events, corticosteroids are not recommended.

TABLE I Laboratory findings for the patient

Parameter	Value	
	Patient	Normal range
Glucose (mg/dL)	471	74–110
HbA1C (%)	7.8	4.6–6.1
C-Peptide (ng/mL)	<0.1	0.8–3.85
Amylase (U/L)	59	37–125
Anti-GAD (IU/mL)	3.0	<10
Anti-ICA (ratio)	0.50	<1
TSH (μUI/mL)	1.02	0.35–4.78
Free T4 (ng/dL)	1.33	0.89–1.76
Anti-TPO (IU/mL)	<28	<70
Anti-Tg (IU/mL)	24	<70
HLA typing	DRB1*11,*13 DQB1*03,*06	

GAD = glutamic acid decarboxylase; ICA = pancreatic islet cell antibodies; TSH = thyroid-stimulating hormone; T4 = thyroxine; TPO = thyroid peroxidase; Tg = thyroglobulin; HLA = human leucocyte antigen.

TABLE II Summary of findings in the associated literature

Report	Sex (M/F)	Disease	Agent	Time to development (months)	Glucose (mg/dL)	Diabetic ketoacidosis	C-Peptide (ng/mL)	HbA1C (%)	Antibodies detected (positivity)
Gaudy *et al.,* 2015[11]	F	Melanoma	Pembrolizumab	<2	909[a]	Yes	Not detected	6.85	None
Hughes *et al.,* 2015[12]	F	Melanoma	Nivolumab	5	532	Yes	<0.1	6.9	None
	F	NSCLC	Nivolumab	<1	350	Yes	<0.1	7.7	Anti-GAD
	M	RCC	Nivolumab	4	340	No	1.3	8.2	Anti-GAD, ICA, IAA
	M	SCLC	Nivolumab	<1	749	Yes	<0.1	9.7	Anti-GAD
	F	Melanoma	Pembrolizumab	<1	703	Ketonuria	0.5	7.4	None
Martin-Liberal *et al.,* 2015[13]	F	Melanoma	Pembrolizumab	<2	NR	Yes	NR	NR	Anti-GAD
Mellati *et al.,* 2015[14]	M	NSCLC	Anti–PD-L1, unspecified	<4	512	Yes	0.3	9.8	None
	F	HNSCC	Anti–PD-L1, unspecified	<2	753[a]	Yes	<0.1	9.4	Anti-GAD
Hansen *et al.,* 2016[15]	M	Melanoma	Pembrolizumab	12	408	NR	2.4	9.7	Anti-GAD
Kong *et al.,* 2016[16]	M	NSCLC	Pembrolizumab	<6	866[a]	Yes	<0.09[b]	7.9	None
Lowe *et al.,* 2016[17]	M	Melanoma	Ipilimumab and nivolumab	<5	NR	Yes	<0.1	NR	Anti-GAD
Miyoshi *et al.,* 2016[18]	F	Melanoma	Nivolumab	<5	531	Yes	0.23	7.3	None
Okamoto *et al.,* 2016[19]	F	Melanoma	Nivolumab	12	580	Ketonuria	1.0	7.0	None
Alhusseini and Samantray, 2017[20]	M	NSCLC	Ipilimumab and pembrolizumab	<1	525	Yes	Not detected	8.5	Anti-GAD
Chae *et al.,* 2017[21]	M	NSCLC	Pembrolizumab	<1	616	No	<0.81	5.8	Anti-GAD, IA2
Godwin *et al.,* 2017[22]	F	NSCLC	Nivolumab	1	739	Yes	<0.1	7.1	Anti-GAD, IAA, IA2
Ishikawa *et al.,* 2017[23]	F	Melanoma	Nivolumab	12	580	NR	1.0	7.0	None
Li *et al.,* 2017[24]	M	NSCLC	Nivolumab	<1	592	Yes	NR	7.2	Anti-GAD
Munakata *et al.,* 2017[25]	M	CHL	Nivolumab	<3	326	No	NR	7.3	None
Teramoto *et al.,* 2017[26]	F	Melanoma	Nivolumab	<8	661	Yes	0.08	8.9	None
Usui *et al.,* 2017[27]	M	NSCLC	Nivolumab	<1	743	Yes	<0.03	6.4	Anti-GAD
	F	NSCLC	Nivolumab	<2	246	NR	NR	6.5	None
Present case	M	NSCLC	Nivolumab	10	471	No	<0.1	7.8	None

[a] Converted from mmol/L.
[b] Converted from nmol/L.
M/F = male or female; NSCLC = non-small-cell lung carcinoma; GAD = glutamic acid decarboxylase; RCC = renal cell carcinoma; ICA = islet cell antibodies; IAA = insulin autoantibodies; SCLC = small-cell lung carcinoma; NR = not reported; HNSCC = head-and-neck squamous cell carcinoma; IA2 = insulinoma-associated protein 2; CHL = classical Hodgkin lymphoma.

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