Precipitation of Autoimmune Diabetes With Anti-PD-1 Immunotherapy

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Immunotherapy targeting T-cell regulatory molecules is highly effective in multiple cancers refractory to standard chemotherapies. However, blocking inhibitory molecules on activated T cells not only increases tumor cell destruction but also can breach tolerance, enabling pathological T cells to react with self-antigens. Indeed, autoimmune endocrinopathies, including hypophysitis, hypopituitarism, and thyroiditis, have been reported in trials involving anti-CTLA-4 and anti-PD-1 monoclonal antibodies (1–3). But autoimmune diabetes has not been definitively linked to these agents.

We describe the development of new-onset insulin-dependent diabetes in five patients after receiving anti-PD-1 antibodies, either as single agent or in combination with other cancer drugs. Clinical history and key laboratory findings are summarized in Table 1. Notably, while the patients presented with diverse cancer types, and some had been treated with other immunological agents, their histories were common for anti-PD-1 antibody exposure prior to developing autoimmune diabetes. Time from drug administration to diabetes onset spanned 1 week to 5 months, when patients presented with severe hyperglycemia or diabetic ketoacidosis (DKA) with elevated HbA_{1c}. Diabetes was a new diagnosis for all but one patient who had preexisting type 2 diabetes controlled with metformin. Most patients exhibited inappropriately low or undetectable C-peptide (Table 1). All were initiated on insulin therapy upon presentation and remained insulin-dependent for glucose control.

Three of the five patients had positive autoantibodies to diabetes autoantigens, with markedly elevated anti-GAD65 titer in patient 4. Among four HLA-$A2^+$ patients, two had increased diabetes antigen-specific $CD8^+$ T cells, consistent with prior findings of such cells in new-onset type 1 diabetes (4,5). The majority of these cells were $CCR7^{-\text{ or }+}$ or $CD45RO^+$ effector or memory cells (66%) (data not shown). Interestingly, two patients also developed autoimmune thyroiditis as manifested by thyroid autoantibodies and abnormal thyroid function tests, consistent with heightened autoimmunity from the immune-enhancing monoclonal antibodies.

We highlight the fact that our patients exhibited both cellular and humoral diabetes-associated autoimmunity, an otherwise rare finding in this age-group (>55 years). Not only do our cases demonstrate temporal correlation between anti-PD-1 treatment and diabetes onset, they also provide the first mechanistic support for cancer immunotherapies targeting T-cell regulatory pathways to precipitate autoimmune diabetes. Other factors that may influence predisposition for hyperglycemia and autoimmunity in our patients included combined use with other immune modulators (patient 1), pancreatic metastases (patient 3), and preexisting type 2 diabetes (patient 4). Nonetheless, the fact that they all developed acute severe hyperglycemia with ketoacidosis or low/undetectable C-peptide levels is strong evidence for a new and insulin-deficient type of diabetes.

Diabetes had previously been reported as an adverse event to anti-PD-L1 (2) and one case was reported in 206 subjects treated with nivolumab (3), but there lacked evidence for an autoimmune mechanism. Our report demonstrates humoral and cellular autoimmunity in multiple patients with anti-PD-1–induced diabetes. While it is difficult to estimate the true incidence of this phenomenon, the five patients in our series represent less than 3% of total subjects who have participated in PD-1/PD-L1 trials at our institution. These cases illustrate the importance of recognizing this potential precipitant of

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Table 1—Clinical history and key laboratory findings

Patient	Age/sex	Primary diagnosis	Pertinent history	Anti-PD-1 drug	Other chemotoxins	Diabetes presentation	Random C-peptide* and glucose	Time after anti-PD-1	Antibody positivity/titers ^	HLA	Diabetes antigen-specific T cells†
1	55/F	Melanoma	Autoimmune thyroid disease	Nivolumab	Ipilimumab, prednisone	DKA, glucose 532 mg/dL, HbA_{1c} 6.9% (52 mmol/mol)	<0.1 ng/mL and 52 mg/dL	5 months	None	$A2.1^+$, $DR4^+$	0.35%
2	83/F	Non–small-cell lung cancer	Remote smoker	Nivolumab	None	DKA, glucose 350 mg/dL, HbA_{1c} 7.7% (61 mmol/mol)	<0.1 ng/mL and 336 mg/dL	<1 month	GAD65/1.2	$A2.1^+$, $DR4^+$	0.28%
3	63/M	Renal cell carcinoma	Hypertension	Nivolumab	Proleukin, bevacizumab, interferon	Random glucose 247, 340 mg/dL; HbA_{1c} 8.2% (66 mmol/mol)	1.3 ng/mL and 79 mg/dL	4 months	GAD65/1.1, ICA512/1.2, Insulin (IAA)/47	$A2.1^+$, $DR4^+$	2.01%
4	58/M	Small-cell lung cancer	Type 2 diabetes	Nivolumab	Carboplatin/ etoposide, paclitaxel	DKA, glucose 749 mg/dL, HbA_{1c} 9.7% (83 mmol/mol) (from 8.5% [69 mmol/mol] prior)	<0.1 ng/mL and 284 mg/dL 0.6 ng/mL and 523 mg/dL	1 week	GAD65/13819	$A2.1^+$	0.89%
5	64/F	Melanoma	Autoimmune thyroid disease, psoriasis	Pembrolizumab	None	Ketonuria, glucose 703 mg/dL, HbA_{1c} 7.4% (57 mmol/mol)	0.5 ng/mL and 268 mg/dL	<1 month	None	$DR4^+$	N/A

*C-peptide reference range: 1.1–4.4 ng/mL. †Patients 1, 2, 3, and 4 were positive for HLA-A2.1 from screening by flow cytometry using monoclonal antibody BB7.1 (Abcam, Cambridge, MA). HLA-A2.1 tetramers were obtained from the National Institutes of Health Tetramer Core Facility (Atlanta, GA) and loaded with peptides from five diabetes antigens: insulin A chain (GIVEQCCTSI), insulin B chain (HLVEALYLV), preproinsulin (ALWMRLLPL), GAD65 (VMNILLQYVV), and IGRP (LNIDLLWSV) (5). Peripheral blood mononuclear cells (PBMCs) were incubated with the five class I diabetes antigen-containing tetramers. The data shown represent positive staining after subtracting staining with a negative tetramer. PBMCs from HLA-$A2.1^+$ donors without diabetes served as negative control and showed staining (mean ± 2 SD) of 0.5%. PBMCs were also stained with monoclonal antibodies to CD45RO, CCR7, and CD45RA to identify cellular phenotypes. Flow data were analyzed using FlowJo software version 9.6.1 (Tree Star, Ashland, OR). ^Diabetic autoantibodies to GAD65, ICA512, and insulin were performed at LabCorp, Burlington, NC. Normal GAD65 titers <0.5 U/mL, ICA512 <1.0 U/mL, and IAA <5.0 U/mL.

autoimmune diabetes in older individuals receiving immunotherapy.

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