



Anti-PD-1 Therapy–Associated Type 1 Diabetes in a Pediatric Patient With Relapsed Classical Hodgkin Lymphoma

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OBJECTIVE

Immune checkpoint inhibitors (ICIs) perturb T-cell regulatory pathways to enhance antitumor immunity. However, an increase reporting of ICI-associated diabetes is observed in adults. To our knowledge, no cases have been reported in the pediatric population.

RESEARCH DESIGN AND METHODS

We describe a pediatric case of ICI-associated type 1 diabetes in a 12-year-old Hispanic boy with Hodgkin lymphoma. The patient had a history of autologous hematopoietic stem cell transplantation and was treated with pembrolizumab after disease progression.

RESULTS

The patient was admitted for diabetic ketoacidosis after five cycles of pembrolizumab. The patient was discharged with daily insulin injections and has continued on exogenous insulin ever since.

CONCLUSIONS

The expanded ICI use may lead to more cases in pediatric patients as has been observed in adults. Considering the acute manifestation of diabetes and the added burden of lifelong insulin therapy, in particular for pediatric patients and their families, monitoring and education of ICI-associated diabetes in children is needed.

Insulin-dependent diabetes associated with immune checkpoint inhibitors (ICIs) is a rare phenomenon but of high clinical significance due to its presentation as potentially life-threatening diabetic ketoacidosis (DKA). In the setting of advanced malignancies, ICI-associated diabetes may seem peripheral, but its chronicity, complications, and daily glucose monitoring and insulin injections drastically alter patients' quality of life and complicate cancer treatment. Moreover, the unprecedented level of interest in immunotherapy research will lead to more widespread use of ICIs and a subsequent increase in diabetes, as evidenced by recent data (1–3). One study reported 283 new cases during a 4-year period, with more than half reported in 2017 (1). The primary cancer types were melanoma (43%), lung (32%), and renal (10%), indicative of early ICI approvals in these tumors. While the nature of ICI-associated diabetes is better defined for melanoma, other malignancies, such as lymphoma, are rarely reported, making it difficult to assess patient characteristics in various types of cancer that are approved for ICI use, especially for hematologic malignancies.

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Cytotoxic T-cell–associated protein 4 (CTLA-4), and programmed death 1 (PD-1) and its ligand, PD-L1, are mediators of inhibitory signals that reduce T-cell activity (4,5). This blunting of T-cell activity plays an important role in maintaining immune tolerance and preventing autoimmunity. Inhibition of CTLA-4– and PD-1/PD-L1–associated immune regulation can activate T-cell response to tumors and increase antitumor immunity but can also precipitate autoimmune diseases (6). Seven ICIs are currently available for various malignancies, two of which are also approved for Hodgkin lymphoma (7).

Herein, we present the first pediatric patient, to our knowledge, who developed ICI-associated type 1 diabetes after short-term pembrolizumab treatment for Hodgkin lymphoma.

RESEARCH DESIGN AND METHODS

A 12-year-old Hispanic boy with a history of autologous hematopoietic stem cell transplantation (aHSCT) for stage III relapsed classical Hodgkin lymphoma was treated with pembrolizumab after disease progression. Multiple new bilateral pulmonary nodules were identified, and the patient was treated with pembrolizumab monotherapy 7 months after transplantation. The CT scan after four cycles of pembrolizumab indicated near resolution of pulmonary nodules.

RESULTS

The patient was admitted for DKA after five cycles of pembrolizumab (4 months after the first cycle). The patient was discharged with daily insulin injections and has continued on exogenous insulin therapy since then. The patient continued with pembrolizumab for three more cycles and subsequently developed hypothyroidism, which was treated with levothyroxine. Pembrolizumab treatment was stopped when the patient underwent a haploidentical bone marrow transplantation (BMT). At the time of this report, the patient was 1-month posttransplantation with standard conditioning and prophylactic treatments. The patient's condition remains stable, with evidence of early engraftment. The patient's glycemic control, however, remains challenging due to ongoing hypoglycemic and hyperglycemic episodes and bruising from subcutaneous injection sites due to thrombocytopenia.

At the time of the patient's cancer diagnosis, he presented with unintentional weight loss and was noted to have prediabetes, with HbA_{1c} of 6.0% and a BMI of 19.7 kg/m², which is at the 75th percentile for BMI-for-age. The patient did not demonstrate any glycosuria or ketonuria during this time. At the start of pembrolizumab therapy, he had a normal random glucose level of 100 mg/dL. Relevant past medical history included asthma and vitamin D deficiency, for which he received treatment with albuterol and vitamin D supplementation. There is no autoimmune disease history in the patient or family, including type 1 diabetes, although there was a non–first-degree family history of type 2 diabetes. The patient presented with acute progression to hyperglycemia, an HbA_{1c} of 8.9%, and a low C-peptide, suggesting a rapid loss of β -cell function. Evaluation of type 1 diabetes-associated autoantibodies at the time of DKA revealed the presence of two autoantibodies, insulin autoantibody and islet antigen 2 (IA-2) antibody (Table 1). The patient also carried HLA-DR4 that predisposes to type 1 diabetes.

CONCLUSIONS

The incidence of insulin-dependent diabetes associated with ICIs in adults is ~1% (7), although it may be underreported due to misdiagnosis. The clinical features of ICI-associated diabetes differ from classic type 1 diabetes: patients are older (age range 22–84 years), more susceptible to DKA (76%), and positive for islet autoantibodies in only ~50% of cases (2). In addition, >70% of patients were positive for type 1 diabetes-risk HLA-DR4, whereas other high-risk HLA alleles, including HLA-DR3, DQ2, and DQ8, were not overrepresented (3). ICI-associated diabetes is most frequent in the context of favorable antitumor therapy (3).

The published cases of ICI-associated diabetes were mostly from melanoma and lung patients owing to the initial ICI approvals. To date, all cases are adult patients, and most are Caucasians, with only two hematologic malignancies. The increasing use of ICIs in clinical practice may increase diabetes incidence across different cancer types, age-groups, and ethnicities. We believe that our case is the first pediatric patient who developed type 1 diabetes after ICI therapy. The presence of islet autoantibodies against insulin and IA-2, rather than GAD65, as is

most frequent in adult type 1 diabetes, latent autoimmune diabetes in adults, or ICI-associated type 1 diabetes, and the apparently rapid progressive loss in β -cell function are consistent with juvenile-onset type 1 diabetes, but distinct from type 1 diabetes in adults (8). However, rapid loss in β -cell function is frequent in ICI-associated diabetes in adults (9). Moreover, our patient has a unique oncologic treatment history before and after ICI therapy that represents novel clinical features. The patient's history of aHSCT before pembrolizumab therapy and allogeneic BMT after ICI-associated diabetes may have modulated the patient's immunologic milieu by uniquely reprogramming tumor and islets microenvironments. This may provide mechanistic insight into the development of his diabetes and potentially uncover therapeutic targets that improve or reverse type 1 diabetes.

aHSCT is a well-established treatment for hematologic malignancies and is increasingly used for refractory autoimmune diseases to halt autoimmune destruction and reestablish tolerance (10). The putative mechanism points to greater diversity in the T-cell repertoire (11), thymus reactivation of regulatory T cells (Tregs) (12), and an increase in the function or number of Tregs (13). The clinical efficacy of aHSCT among patients with type 1 diabetes was remarkable, with most achieving long-term insulin independence (13,14). Our patient, who had no history of autoimmunity but carried high-risk HLA-DR4 and had prediabetes, underwent aHSCT before pembrolizumab therapy. The aHSCT targeted to treat our patient's cancer may have unintentionally provided a more favorable environment for immune tolerance given his genetic disposition for type 1 diabetes. In theory, even with aHSCT-treated immune reset, inhibiting the PD-1/PD-L1 signaling pathway still played a significant role in precipitating overt diabetes by activating autoreactive cytotoxic T cells and reducing the Treg number and functions required for immune tolerance maintenance.

Short-term pembrolizumab treatment, despite its adverse events of diabetes and hypothyroidism, had an excellent radiographic response that showed near resolution of pulmonary nodules for his relapsed Hodgkin lymphoma. The patient underwent a haploidentical BMT 6 months after developing diabetes. The role of the second transplantation and

Table 1—Clinical and biochemical assessment

Parameter	HL diagnosis	DKA presentation (25 months after HL)	6 months after DKA	1 month after allogeneic BMT	Reference
Glucose (random)	100	347	181	214	80–128 mg/dL
HbA _{1c}	6.0	8.9	8.7	—	<6.5%
C-peptide	—	0.3	<0.1	<0.1	0.8–3.5 ng/mL
Islet cell antibodies	—	—	<1:4	—	<1:4
Insulin autoantibody	—	7.4	—	—	<0.4 units/mL
IA-2 antibody	—	8	—	—	<5.4 units/mL
GADA	—	<5.0	<5.0	—	<5.0 IU/mL
HLA genotype	—	—	DR4	—	N/A
Vitamin D, 25-hydroxy	21	—	—	39	30–100 ng/mL
Thyroid stimulating hormone	—	1.28	4.8	—	0.40–4.00 μ IU/mL

GADA, glutamic acid decarboxylase antibody; HL, Hodgkin lymphoma; N/A, not applicable.

that of donor's immune cells in our patient has yet to be determined, especially in its implication on halting autoimmune destruction of residual β -cells and inducing immune tolerance.

Early pediatric ICI clinical trials have demonstrated only limited clinical response and, with the exception of Hodgkin lymphoma, results have been mainly ineffective compared with remarkable benefits observed in adult cancers. As a result of the significantly lower mutational load in pediatric cancers, combination therapy of multiple checkpoint inhibitors is recommended (15), which may increase the use of ICIs in the pediatric population and subsequent adverse events. Considering the acute manifestation of diabetes and the added challenge of daily glucose monitoring and insulin injections in pediatric cancer patients and their families, balancing the benefit and risk of ICI therapy is needed, especially before exhausting all other potential curable therapies such as BMTs. Additionally, screening strategies should be adopted before ICI use to assess risk for developing diabetes, especially HLA genotype and type 1 diabetes-associated autoantibodies.

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