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Polyendocine autoimmunity and DKA following anti-PD-1

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Abstract

Immune checkpoint inhibitor (ICI) therapies are now first line therapy for many advanced malignancies in adults, with emerging use in children. With increasing ICI use, prompt recognition and optimal management of ICI-associated immune related adverse events (IRAEs) is critical. Nearly 60% of ICI-treated adults develop IRAEs, which commonly manifest as autoimmune skin, gastrointestinal, and endocrine disease and can be life-threatening. The incidence, presentation, and disease course of spontaneous autoimmune diseases differ between adults and children, but the pattern of pediatric IRAEs is currently unclear. We report a case of a pediatric patient presenting with new onset autoimmune diabetes mellitus and diabetic ketoacidosis during ICI treatment for fibrolamellar hepatocellular carcinoma (FLC). Distinct from spontaneous type 1 diabetes mellitus (T1DM), this patient progressed rapidly and was negative for known beta cell autoantibodies. Additionally, 21-hydroxylase autoantibodies were positive suggesting development of concomitant adrenal autoimmunity. Current guidelines for the management of IRAEs in adults may not be appropriate for the management of pediatric patients, who may have different autoimmune risks in a developmental context.

Table of Contents Summary:

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Contributors' Statement Page

Drs. Dasgupta and Tsay conceptualized the report, analyzed and interpreted clinical data, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Federman, Lechner, Su conceptualized the report, analyzed and interpreted clinical data, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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A case of a pediatric patient presenting with new onset autoimmune diabetes mellitus and diabetic ketoacidosis during immune checkpoint inhibitor treatment for fibrolamellar hepatocellular carcinoma.

Keywords

Diabetes Mellitus; Immune Checkpoint Inhibitor Immunotherapy; Autoimmunity

Introduction

Immune checkpoint inhibitors (ICIs) have shown great promise in the treatment of advanced cancers by stimulating the body's own immune system to attack cancer cells. Specifically, ICIs block the regulatory proteins programmed cell death protein-1 (anti-PD-1) or its ligand (anti-PD-L1) or cytotoxic T lymphocyte associated-4 (anti-CTLA-4) to increase T cell activation[1]. Since their initial FDA approval for metastatic melanoma in 2011, ICIs have shown durable responses in multiple adult cancers, including non-small cell lung cancer, Hodgkin lymphoma, kidney and bladder cancer, and head and neck cancer in[2]. Currently, 19 cancers are FDA-approved for treatment with ICIs[3], and >40% of adult cancer patients are now eligible for ICI therapy[4].

While there has been limited efficacy and safety data in pediatric patients, there is ongoing interest in expanding the use of ICIs in this population[1,2,5–7]. Based on adult data, anti-PD1 was recently approved by the FDA for the treatment of classical Hodgkin lymphomas in children[2,8]. Currently, trials are either underway or planned for B-cell acute lymphoblastic leukemia, ependymoma, Ewing sarcoma and other treatment resistant cancers (Clinicaltrials.gov, NCT04546399, NCT04730349).

As ICI use continues to increase[4], there is an urgent need for clinicians involved in the care of these patients to recognize ICI-associated immune related adverse events (IRAEs). In adults, grade 3–4 IRAEs develop in 40% of patients treated with combination ICIs (anti-PD-1 and anti-CTLA-4)[9], which can manifest as immune-mediated destruction of multiple tissues (e.g. skin, gut, endocrine organs, lung, heart, nervous system). IRAEs can have a significant clinical impact including interruption of cancer treatment, permanent organ dysfunction, hospitalization, and even premature death.

It is now well-recognized that immune responses in children differ from that in adults[10,11]. The development of spontaneous type 1 diabetes mellitus (T1DM), for example, occurs more frequently in the pediatric (34.3 cases per 100,000 persons) compared to adult population (18.6 cases per 100,000)[12]. Whether distinct IRAE patterns will be seen in pediatric patients, however, remains unknown. Here we report a pediatric patient with hepatic cancer undergoing ICI treatment who presented with a potentially life-threatening IRAE.

Case

The patient is a 14-year-old female with fibrolamellar carcinoma (FLC) who developed altered mental status in the setting of fatigue, polyuria, polydipsia and headache for 1 week. The patient was found to have a blood glucose of >900 mg/dL, pH of 6.9, serum bicarbonate level <5 mEq/L, and beta-hydroxybutyrate level of 14.2 mmol/L. She was diagnosed with severe diabetic ketoacidosis (DKA) and admitted to the pediatric intensive care unit (ICU).

Eight months prior, the patient was diagnosed with FLC. She underwent a right hepatic lobectomy for a 14 cm liver mass, and received 6 cycles of systemic therapy with nivolumab (anti-PD1), pegylated interferon alpha, and capecitabine[13]. After the initiation of therapy, monitoring laboratory data showed normal serum blood glucose levels, electrolytes, and thyroid function up to 4 weeks before DKA presentation. An elevated random serum blood glucose level of 221 mg/dL was noted two weeks prior to presentation.

Laboratory evaluation during her hospitalization for DKA revealed a low c-peptide level and glycated hemoglobin (HbA1c) of 9.0% (compared to average 13.1% in new-onset T1DM patients who present in DKA)[14]. Autoantibodies for diabetes were negative [Table 1]. The patient was treated over the course of 3 days with intravenous insulin and fluids. With resolution of her DKA, she transitioned to subcutaneous insulin and was discharged. C-peptide repeated two weeks later remained undetectable. Her cancer treatment has been monitored by the immune response evaluation criteria in solid tumours (iRECIST) criteria and has been stable. She has continued on immunotherapy and remains insulin dependent.

Treatment with ICIs can lead to multiple co-occurring IRAEs[15]. Thyroid function tests showed low TSH and low FT4, and thyroid peroxidase and thyroglobulin antibodies were negative. TSH and FT4 normalized two weeks later, following resolution of acute illness, indicating likely nonthyroidal illness. ACTH and cortisol levels were normal, and she did not have symptoms of adrenal insufficiency. However, 21-hydroxylase antibodies were positive, which are correlated with the development of autoimmune primary adrenal insufficiency (i.e. Addison's disease)[16].

Discussion

We report a case of a pediatric patient presenting with DKA from new-onset T1DM and evidence of primary adrenal autoimmunity secondary to ICI therapy. This case highlights an emerging and potentially life-threatening diagnosis in pediatric patients. Importantly, the presentation of ICI-associated IRAEs, including ICI-T1DM, is distinct from usual spontaneous autoimmune disease seen in childhood. First, the pace of T1DM disease progression was more rapid, consistent with what has been reported in adults with ICI-associated T1DM[15]. Adult patients often have hyperglycemia and low or undetectable c-peptide at presentation, but HbA1c is only modestly elevated. In a case series of 91 adult patients with ICI-T1DM, the median HbA1c at diagnosis was 7.7% with a range of 5.4–11.4%[17]. Additionally, 50 to 71% of patients with ICI-T1DM present in DKA[17,18]. Together these findings suggest that patients are often critically ill at presentation, yet the average blood glucose has not been elevated for a prolonged period. Moreover, in an

ICI-treated patient with evidence of hyperglycemia and hypoinsulinemia, a normal HbA1c does not exclude new-onset T1DM. Second, autoantibodies that characterize early stages of spontaneous T1DM may not be present in ICI-T1DM. Islet antibodies are positive in only 53% of patients, compared to classic T1DM, where autoantibodies are present in 80–95% of patients at diagnosis[17]. We therefore recommend that new hyperglycemia workup in ICI-treated pediatric patients include a c-peptide level to assess beta cell insulin production.

Incident ICI-T1DM is relatively rare in adults (approximately 1% of ICI treated patients)[17]. One other pediatric case of ICI-T1DM has recently been reported in a 12-year-old patient with Hodgkin lymphoma treated with single agent anti-PD-L1[19]. Pediatric patients may be at increased risk for ICI-T1DM, compared to adult patients, given the increased incidence of spontaneous T1DM in children compared to adults. The patient presented here is, to our knowledge, the first known case of ICI-T1DM in a patient on triple therapy with nivolumab, interferon-alpha, and capecitabine. Combination ICI therapy (i.e. anti-PD-1 plus anti-CTLA-4) has an increased risk of IRAEs in adults, and perhaps pediatric patients. Interferon alpha therapy has also been associated with the development of T1DM with an estimated prevalence of interferon treatment-related T1DM of 0.34%[20]. Early analyses from patients undergoing triple therapy[13], as well as studies of patients being treated with checkpoint inhibitors in combination with interferon alpha, show high rates of IRAEs, but no reported cases of T1DM[21,22].

The presence of one IRAE should increase providers' suspicion for another. In adult patients diagnosed with ICI-T1DM, two thirds were diagnosed with another IRAE[15]. Our patient had 21-hydroxylase antibodies, raising concern for autoimmune primary adrenal insufficiency (PAI). While her ACTH and cortisol levels were normal, she will be screened regularly for the development of adrenal insufficiency (AI). ICI-related PAI is rare[2], as AI is typically secondary to hypophysitis. Morning ACTH and cortisol levels and serum electrolytes can help to distinguish primary from secondary AI. Imaging of the adrenal gland and pituitary can also be considered, though the absence of pituitary enhancement does not exclude ICI-hypophysitis [2]. While uncommon, a recent study identified 45 cases of definite ICI-related PAI and 406 suspected cases[23]. More than 90% of these cases were associated with severe complications defined as life-threatening hospitalization or physical disability; death was observed in 7.3% of cases. The pathophysiology of ICI-PAI remains unclear as cases have been associated with adrenal antibodies, adrenal atrophy, and adrenalitis. Of three reported cases of ICI-related PAI with antiadrenal antibodies[24–26], patients all presented in adrenal crisis and with other endocrine IrAEs (e.g. thyroiditis, T1DM). Furthermore, as our case highlights, while PAI is considered exceedingly rare in adult patients, the prevalence in pediatric patients may be higher given the underlying differences in autoimmune risk and pathogenesis. Given the high morbidity and mortality associated with ICI-associated IRAEs, protocols are needed to screen for type 1 diabetes, adrenal insufficiency, thyroid dysfunction, and other IRAEs in pediatric patients on ICI, as has been suggested for adults[33].

This case highlights areas of continued uncertainty in pediatric cancer patients treated with ICI. The frequency and type of biomarkers used for routine screening of IRAEs in pediatric patients remain to be defined. This will require a deeper understanding of the organs most often affected by IRAEs and median time to onset after initiation of ICI

treatment, which may differ from adult patients. Should ICI treatment continue in pediatric patients with IRAEs? Current recommendations suggest that for endocrine IRAEs in adults, ICI therapy should be continued. Furthermore, the use of high dose glucocorticoids or withdrawal of ICI treatment is unlikely to reverse permanent organ damage and may be associated with increased mortality[27–29]. For non-endocrine IRAEs, a number of treatment strategies are recommended and continue to evolve, with the consideration for non-steroid therapies[33]. It remains unclear whether adult guidelines can be safely extended to pediatric patients. Furthermore, it is now clear in adults that the development of IRAEs is associated with improved cancer response to immunotherapy[30–32]. This relationship is stronger for patients who develop multiple, higher grade, and endocrine IRAEs[32]. By stopping cancer immunotherapy for IRAEs, therefore, we may be limiting anti-cancer benefits. Balancing toxicity with efficacy is an ongoing challenge in ICI treatments that requires additional study of the mechanisms underlying IRAE development. It will be important that such future research include pediatric patients.

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Table I.

Laboratory Values

Parameter	At DKA	2 weeks after DKA	Reference
HbA1c	9.0%		
C-peptide	0.2	<0.2	1.1–4.3 ng/mL
GAD antibody	<5.0		0–5.0 IU/mL
Insulin autoantibody	<0.4		0.0–0.4 U/mL
IA-2 antibody	<7.5		<7.5 U/mL
ZnT8 antibody	11		<15 U/mL
ICA antibody, IgG		<1:4	<1:4
TSH	0.35	1.3	0.3–4.7 mcIU/mL
Free T4	0.5	1.2	0.8–1.7 ng/dL
Cortisol (8AM)	12		8–25 mcg/dL
ACTH	17		4–48 pg/mL
21-hydroxylase antibodies	Positive		Negative

DKA, diabetic ketoacidosis; GAD, Glutamic Acid Decarboxylase; IA-2, Islet antigen 2; ZnT8, Zinc Transporter 8; ICA, Islet Cell Cytoplasmic