BRIEF REPORT

NEW-ONSET DIABETIC KETOACIDOSIS SECONDARY TO NIVOLUMAB THERAPY IN A PATIENT WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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KEYWORDS:

Autoimmune

Diabetic ketoacidosis

Hyperglycemia

Insulin

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ABSTRACT:

Introduction: Inhibitors of programmed cell death receptor (PD-1) and its ligand (PD-L1), such as nivolumab and pembrolizumab, confer anti-autoimmune activities and are therefore approved for anti-cancer therapy. Their mode of action removes autoimmunity checkpoints, thus increasing the risk of immune-related adverse events.

Case Presentation: This report describes a clinical case of life-threatening diabetic ketoacidosis (DKA) in a patient after long-term nivolumab administration to treat primary central nervous system lymphoma (PCNSL). The patient presented to the emergency department (ED) with symptoms of fatigue, along with nausea and vomiting for two days; laboratory testing revealed significant hyperglycemia (glucose 673 mg/dL), elevated anion gap (>27), metabolic acidosis, ketonemia, glucosuria and ketonuria, findings of which were consistent with DKA. Given no personal history of diabetes mellitus or other autoimmune conditions and additional tests ruling out alternative causes, the patient was suspected of having newly-onset DKA secondary to nivolumab treatment.

Management & Outcome: The patient was treated with fluids, electrolytes replenishments and insulin drip, which closed the anion gap and normalized electrolytes. She was transitioned to subcutaneous insulin. The patient recovered well and was discharged on Metformin and long-acting insulin, with close follow-up with endocrinology and oncology.

Discussion: Autoimmune endocrinopathies induced by checkpoint inhibitors for cancer treatment have been reported in the past. Newly-onset hyperglycemia and DKA are common autoimmune-mediated side effects of checkpoint inhibitor uses in patients without prior history of diabetes mellitus. Clinicians should be aware to prevent this potentially life-threatening condition.

INTRODUCTION

Cancer cells can evade the host's immune-mediated programmed cell death (apoptosis) signals. Programmed cell death receptor (PD-1) and its ligand (PD-L1) function as an inhibitory immune checkpoint for the activity of peripheral T-lymphocytes (T-cells) upon their interaction.[1] The checkpoint confers immunologic tolerance, which is essential for preventing the onset or progression of autoimmune disease.[2] A wide variety of immune cells present in tumor or cancer microenvironments, particularly tumor-reactive T-cells, B-cells, natural killer (NK) cells and activated monocytes, exhibit elevated levels of PD-1. PD-L1 binds tumor-reactive T-cells expressing PD-1 (CD279), thus tolerizing them by reverse signaling through T-cell-expressed CD80. This neutralizes the host's anti-tumor immune (CD8+ T-cell) and Fas Ligand-mediated lysis signaling.[3] Using PD-1/PD-1L as therapeutic targets, cancer immunotherapies that help restore anti-cancer immune responses have been developed. They include monoclonal antibodies against PD-1 (nivolumab and pembrolizumab) and the PD-L1 (avelumab, atezolizumab and durvalumab); with only nivolumab and pembrolizumab being

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approved for the treatment of advanced non-small-cell lung cancer (NSCLC), melanoma, Hodgkin's lymphoma and bladder urothelial cancer including renal cell carcinoma (RCC) and other cancers.[4,5,6] Nivolumab, a PD-1 inhibitor, has been demonstrated to be effective against NSCLC, melanoma, RCC, head and neck cancer and Merkel cell carcinoma.[1,6] Both PD-1 and PD-1L confer their immunogenic effects by binding and inhibiting PD-1/PD-1L interactions, thereby preferentially reactivating tumor-reactive T-cells with high specificity for cancer.[7]

However, PD-1/PD-1L inhibitors also remove the essential inhibitory autoimmune checkpoints, thus increasing the risk of immune-related adverse events (AE). A recent systematic review and meta-analysis have demonstrated increased rates of autoimmune endocrinopathies, including hypophysitis (Odds Ratio—OR: 3.38, 95% CI: 1.02 to 11.08), adrenal insufficiency, thyroid disorders—hypothyroidism (OR: 7.56, 4.53 to 12.61), pneumonitis (5.37, 2.73 to 10.56) and colitis (2.88, 1.30 to 6.37), following long-term administration of nivolumab compared to standard treatments.[4] Nivolumab can induce autoimmune diabetes characterized by severe hyperglycemia or diabetic ketoacidosis (DKA).[5,8] This report presents a clinical case of a 55-year-old female patient who presented to the emergency department (ED) with new-onset DKA, suspected to be induced by long-term nivolumab treatment for her primary central nervous system lymphoma (PCNSL).

CLINICAL PRESENTATION

A 55-year-old female with PMHx of PCNSL (status post-intermittent immunomodulatory treatment and stereotactic brain biopsy) presented to the ED with two days of generalized weakness and nausea with non-bloody non-bilious vomiting whenever she tried to eat. She also reported burning chest pain accompanied by intermittent palpitations. She denied fever, chills, headache, dizziness, cough, shortness of breath, abdominal pain, diarrhea, constipation and dysuria. Physical exams revealed that she had no acute distress as she laid calmly in bed. She was neuro-alert and oriented, with no focal deficits. HEENT was normal. Her mucous membranes were moist, no pharyngeal erythema or exudates; neck was supple and with no cervical lymphadenopathy and no facial flushing/redness. A heart exam revealed a regular rate and rhythm, S1S2 without murmurs, gallops or rubs. Her lungs were clear to auscultation bilaterally, with no wheezes, rales or rhonchi. The abdomen was soft, depressible, non-distended with normal bowel sounds, non-tender to palpation. Exams of lower extremities revealed no peripheral edema bilaterally with normal distal pulses. Her skin was normal without rash, generally warm and dry. In the ED, her vital signs were normal except for mild tachycardia and hypertension: 36.5°C, HR 106, BP 141/76, RR17 and oxygen saturation 97% on room air. Her clinical presentation prompted laboratory and imaging investigations.

LABORATORY INVESTIGATIONS AND FINAL DIAGNOSIS

Laboratory results (Table 1) revealed leukocytosis with left shift (WBC 29.1), abnormally low serum electrolytes (Na 126, Cl 90 and HCO3 <9.0) and significant hyperglycemia (673 mg/dL); ABG revealed low pH (7.298), low pCO2 (26.5mmHg), elevated pO2 (125.0 mmHg) and low HCO3 (12.6mmol/L). There was also an anion gap of >27, which suggested high anion gap metabolic acidosis. Urinalysis showed glucose >500 and moderate ketones. Blood cultures were drawn as well. No other precipitating factors were identified. The patient denied a medical history of diabetes mellitus or any use of steroids. She was admitted to MICU to manage a suspected new-onset DKA secondary to long-term nivolumab therapy (two years) for her PCNSL. Endocrinology was consulted and ordered GAD 65 antibody, β-hydroxybutyrate and C-peptide; results showed negative GAD antibody, low β-hydroxybutyrate (< 4.0) and low C-peptide (0.12).

TABLE 1:

Relevant laboratory results drawn at admission

Venous blood gas		**Blood cell count**	
pH	7.03	Hgb (g/dL)	15.3
Arterial blood gas		Hct (%)	45.1
pH	7.298	WBC (×109/L)	29.10
pCO2 (mmHg)			
pO2 (mmHg)	26.5		
125.0	Platelet (x 109/L)	236	
HCO3 (mEq/L)	12.6		
Serum electrolytes		**Endocrine**	
Na (mmol/L)	126	HgA1c	6.4
K (mmol/L)	4.4	β-HB (mg/dL)	>4.5
Cl (mmol/L)	90	GAD-65 Ab	Negative
HCO3 (mmol/L)	<9	C-peptide	0.12
Anion gap	26	**Urine analysis**	
Glucose (mg/dL)	673	Glucose(mg/dL)	≥500
Ca (mg/dL)	8.3	Ketones	Moderate
Mg (mg/dL)	2.1	Protein (g/dL)	Nil
Phos (mg/dL)	2.2		

β-HB, beta-hydroxybutyrate; Ca, calcium; Cl, chloride; GAD-65 Ab, glutamic acid decarboxylase antibody; HCO3, bicarbonate; Hct, hematocrit; Hgb, hemoglobin; HgA1c, glycosylated hemoglobin; K, potassium; Mg, magnesium; Na, sodium; pCO2, partial carbon dioxide pressure; pO2, partial oxygen pressure; Phos, phosphorus; WBC, white blood cells.

MANAGEMENT AND OUTCOME

After initial laboratory confirmation of DKA, the patient was placed on IV hydration (NS boluses, which then transitioned to D5 ½ NS) and insulin drip (titrated according to protocol). Electrolytes were also replenished accordingly. The patient was transferred to the medical floor once being stabilized with a resolution of metabolic derangements. She was then started on mealtime insulin aspart (NovoLog®) and bedtime insulin glargine (Lantus®) injected subcutaneously upon normalization of anion gap, electrolytes and blood glucose. Regarding initial leukocytosis

(WBC 29.1) prior to admission, the patient received one dose of antibiotic (Cefepime) in the ED. However, CXR, UA and blood cultures were negative for any infectious etiologies and antibiotic was discontinued. WBC trended down without further use of antibiotics. This was unlikely the trigger for her ketoacidosis. The patient responded well to treatments, with a resolution of symptoms (nausea, emesis and abdominal discomfort) even after diet advancement. She was hemodynamically stable at the time of discharge. She was discharged on Metformin and Lantus® with follow-up recommendations with the endocrinologist and oncologist to manage central nervous system lymphoma with DKA.

DISCUSSION

This clinical case is among several other clinical cases of new-onset DKA secondary to cancer treatment with checkpoint inhibitors such as nivolumab.[9,13] The Naranjo Algorithm Assessment (Table 2) was used to assess for the likelihood of whether this patient's adverse drug reaction (ADR) of DKA was actually due to nivolumab rather than the result of other factors. The patient in our case received a final Naranjo score of 6, which is interpreted as a probable ADR.

In previously published and current case reports, the involved patients have no history of DM or hyperglycemia and only developed DKA after using checkpoint inhibitors. The overall evidence from these case reports strongly supports that DKA is a common autoimmune-mediated adverse effect induced by checkpoint inhibitors. While it appears that other common autoimmune endocrinopathies produced by checkpoint inhibitors—such as hypophysitis, adrenal insufficiency, thyroid disorders (hypothyroidism), pneumonitis and colitis—are well tolerated,[4,5] clinicians should be aware of the acute nature and severity of the autoimmune DKA. Immediate drug-induced hyperglycemia and autoimmune DKA has been reported in a case report by Aziz *et al*., where a 48-year-old woman with no previous personal history of diabetes or previous use of potential diabetogenic corticosteroids presented with pembrolizimab-induced DKA barely two weeks after a single cycle of the therapy (2mg/kg).[9] Other similar case reports have demonstrated an immediate onset after the patient received only two cycles of nivolumab,[10] and only three cycles of nivolumab.[13] In contrast, others have reported delayed onsets after one year[5] or up to a couple of years, as with this clinical case reported in the current study, where acute autoimmune DKA occurred after two years nivolumab use. Stamatouli *et al*. demonstrated that the time to onset of acute autoimmune DKA presentation was longer than other common AEs, for which on average occur after one–three cycles of treatment or between three–eight weeks after treatment.[11] DKA should always be considered one of the differential diagnoses for patients presenting with metabolic acidosis following treatment with checkpoint inhibitors. Where indicated, oncologists should consider modification or even discontinuation of cancer therapies involving checkpoint inhibitors, especially in cases of immediate onset of acute autoimmune DKA.

CONCLUSION

Immunomodulating therapies have demonstrated good efficacies in the management of multiple cancers. Discussing common AEs and potential acute autoimmune hyperglycemia and DKA with patients who are good candidates for checkpoint inhibitors is an ideal informed consent process. At the same time, clinicians should closely monitor such patients for potential drug-induced DKA, among other immune-mediated AEs.

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TABLE 2:

Naranjo adverse drug reaction probability scale

QUESTION	Yes	No	Do not know	Score
1. Are there previous conclusive reports on th is reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	–1	0	+2
3. Did the adverse reaction improve when the drug was discontinuedor a specific antagonist was administered?	+1	0	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	–1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	–1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	+1	+1	0	0
7. Was the drug detected in blood (or other fluids) in conentrations know to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less seevere when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same os similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	TOTAL SCORE			6

Modified from: Naranjo CA *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239245.

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