Isolated Adrenocorticotropic Hormone Deficiency Associated with Severe Hyperkalemia During Pembrolizumab Therapy in a Patient with Ureteral Cancer and an Ileal Conduit: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Female, 78-year-old
Final Diagnosis: Isolated adrenocorticotropic hormone deficiency
Symptoms: Anorexia • general weakness • muscle pain
Medication: Hydrocortisone
Clinical Procedure: Endocrine test
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course
Background: Immune checkpoint inhibitors (ICIs) are anticancer medications that enhance the antitumor immune response. The clinical benefit afforded by ICIs, however, can be accompanied by immune-related adverse events (IRAEs). One of the common endocrine IRAEs is hypophysitis, which often causes hypopituitarism with secondary adrenal insufficiency (AI). Secondary AI, including isolated adrenocorticotropic hormone (ACTH) deficiency (IAD), is often associated with hyponatremia. Here, we report an unusual case of ICI-related IAD associated with severe hyperkalemia.
Case Report: A 78-year-old woman who had an ileal conduit, chronic kidney disease, type 2 diabetes mellitus, and hypertension and was taking an angiotensin II receptor blocker began treatment for advanced ureteral cancer with the anti-programmed cell death protein 1 inhibitor pembrolizumab. The therapy effectively controlled the cancer, but 4 1/2 months after starting it, the patient developed anorexia, general weakness, and muscle pain and was diagnosed with IAD associated with severe hyperkalemia and hyperchloremic metabolic acidosis. She recovered after prompt administration of corticosteroids and treatment with sodium bicarbonate, glucose/insulin, and cation exchange resins.
Conclusions: Hyperkalemia is a common symptom of primary AI but is less common in patients with central AI because a lack of ACTH does not cause aldosterone deficiency and mineralocorticoid action is preserved. The present case demonstrates the need for physicians to be aware of severe hyperkalemia as a life-threatening complication of secondary AI induced by ICIs, particularly in patients with predisposing factors, such as kidney dysfunction, diabetes mellitus, an ileal conduit, and renin-angiotensin-aldosterone system inhibitor use.

Keywords: Adrenal Insufficiency • Diabetes Mellitus • Hydrocortisone • Hyperkalemia • Renal Insufficiency, Chronic • Urinary Diversion

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/931639

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Background

Immune checkpoint inhibitors (ICIs) are anticancer medications that enhance the antitumor immune response by blocking negative regulators of T-cell function. The clinical benefit afforded by ICIs, however, can be accompanied by immune-related adverse events (IRAEs) that involve different organs, as well as the endocrine system [1]. One of the major endocrine IRAEs is hypophysitis, which often causes hypopituitarism associated with secondary adrenal insufficiency (AI) and can be fatal if not appropriately treated.

Hypophysitis is less frequent and exhibits a distinct clinical phenotype in patients treated with anti-programmed cell death protein 1 (PD-1) inhibitors compared with anti-cytotoxic T-lymphocyte antigen-4 inhibitors [2]. The time of onset of hypophysitis in patients on PD-1 inhibitors is longer, ranging from several months to years, and the symptoms are less severe. Patients do not usually present with headache or fever, and magnetic resonance imaging (MRI) of the sellar region usually does not reveal any abnormality, such as pituitary enlargement. Even in the absence of typical hypophysitis symptoms, however, PD-1 inhibitors often cause hypopituitarism with secondary AI [2,3]. In particular, many cases of isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) [4,5] have been reported [6-31]. Patients with anti-PD-1-related IAD present with cortisol deficiency symptoms, including anorexia, fatigue, and general weakness. In addition, hyponatremia is often a principal sign of anti-PD-1-induced IAD [8].

We report an unusual case of anti-PD-1-related IAD presenting with severe hyperkalemia. In addition, we review previously reported cases of IAD associated with PD-1 inhibitor therapy.

Case Report

A 78-year-old woman with advanced ureteral cancer who was on PD-1 inhibitor therapy with pembrolizumab was admitted to our hospital in November 2019 after experiencing anorexia, general weakness, and muscle pain for several days. The patient had a paternal family history of type 2 diabetes mellitus (T2D), hypertension, and cerebral infarction. She patient did not drink alcohol or smoke cigarettes. She was diagnosed with T2D, dyslipidemia, and hypertension associated with obesity at age 63 years and started medications, including the angiotensin II receptor blocker candesartan. She also had mild chronic kidney disease (CKD) associated with these metabolic disorders.

At the patient's regular check-up in June 2018, a urine culture was positive for occult blood. Abdominal ultrasound, computed tomography (CT), and MRI revealed tumors in the bladder and the left lower part of the ureter. In August 2018, the patient underwent a laparoscopic left total nephroureterectomy, total cystectomy, and ileal conduit urinary diversion. Histopathological examination revealed invasive urothelial carcinoma in the bladder and left ureter. After surgery, the patient's kidney function partially deteriorated, and her serum creatinine levels were 1.5 to 2.0 mg/dL. She also developed mild hyperkalemia and started treatment with dietary potassium restriction and oral calcium polystyrene sulfonate (30 g/d). In addition, she was presumed to have hyperchloremic metabolic acidosis (HMA) associated with her ileal conduit [32].

A CT scan performed in March 2019 detected metastasis in the left pelvis. The patient received 3 courses of chemotherapy with gemcitabine and carboplatin from April to June 2019 and then started maintenance chemotherapy with pembrolizumab (200 mg every 3 weeks) in early July 2019. Her morning plasma ACTH and cortisol levels just before starting pembrolizumab were normal (43.1 pg/mL and 12.5 µg/dL, respectively) (**Table 1**).

After 2 cycles of pembrolizumab therapy, in mid-August 2019, a blood test performed at noon showed a low plasma cortisol level of 5.4 µg/dL (ACTH, 19.4 pg/mL), indicating possible AI. A rapid ACTH stimulation test revealed a slightly low plasma cortisol level (17.1 µg/dL) (**Table 2A**) [33]. However, the patient presented with no symptoms suggestive of hypophysitis or AI, such as headache, fever, anorexia, or general weakness. A brain MRI detected no abnormality in the pituitary gland (**Figure 1A, 1C**). Therefore, she was closely followed with no corticosteroid replacement therapy.

In late August 2019, the patient's morning plasma cortisol level returned to normal (12.2 µg/dL) (**Table 1**). She continued the pembrolizumab therapy, which effectively controlled her ureteral cancer and left pelvic metastasis. A CT performed in September 2019 revealed that the pelvic tumor was smaller and there were no new lesions. In November 2019, however, 5 days after the seventh cycle of pembrolizumab therapy, the patient developed anorexia, general weakness, back pain, and muscle pain in her extremities. In a few days, she had difficulty walking and was admitted to our hospital.

On admission, the patient's body length, weight, temperature, blood pressure, and pulse rate, were 149.0 cm, 58.1 kg, 36.7°C, 99/54 mmHg, and 84 beats/min, respectively. Her mouth was slightly dry. No thyromegaly, heart murmurs, chest rales, abdominal pain, rash, skin pigmentation, or peripheral edema were detected. A blood gas analysis indicated metabolic acidemia (pH 7.204) associated with a low bicarbonate ion (HCO_3) level (13.0 mmol/L) and a normal anion gap (9.8 mmol/L). Blood chemistry results revealed high levels of serum potassium (6.3 mEq/L) and chloride (113 mEq/L) but a low serum sodium level

Table 1. Serial changes in levels of morning plasma adrenocorticotropic hormone and cortisol, serum electrolytes, and blood eosinophils, immediately before and during pembrolizumab therapy in 2019. All blood samples were collected in the morning.

	Early July	Late July	Mid-Aug	Late Aug	Mid-Sept	Early Oct	Late Oct	Late Nov
ACTH (pg/mL)	43.1	45.4	22.8	42.2	62.2	68.3	71.2	16.6
Cortisol (µg/dL)	12.5	11.7	7.4	12.2	12.4	10.3	11.4	1.4
Sodium (mEq/L)	144	141	142	143	144	142	142	134
Potassium (mEq/L)	5.3	5.4	5.2	5.1	4.5	4.6	4.3	6.3
Chloride (mEq/L)	114	114	117	118	118	116	114	113
Creatinine (mg/dL)	1.58	1.94	1.77	1.78	1.90	1.95	1.83	1.79
Eosinophils (/µL)	139	160	141	159	244	271	316	437
White blood cells (/µL)	3400	3800	4400	3700	3700	4100	4000	4200

All blood samples were collected in the morning.

Table 2. Endocrinological investigation.

A: Rapid adrenocorticotropic hormone stimulation test.

		Time (min)		
		Basal	30	60
August 2019	Cortisol (µg/dL)	7.4	14.6	17.1
November 2019	Cortisol (µg/dL)	1.4	6.2	8.5

Tetracosactide acetate (0.25 mg) was administered i.v. in the morning.

B: Corticotropin-releasing hormone (CRH)/growth hormone-releasing factor (GRF)/thyrotropin-releasing hormone (TRH)/luteinizing hormone-releasing hormone (LHRH) stimulation test (November 2019).

	Reference range*	Basal	Peak (time at peak)
Adrenocorticotropic hormone (pg/mL)	7.2-63.3	11.6	16.7 (60 min)
Cortisol (µg/dL)	7.1-19.6	2.2	2.9 (90 min)
Growth hormone (ng/mL)	0-2.47	1.5	13.6 (15 min)
Thyroid-stimulating hormone (µIU/mL)	0.50-5.00	2.86	19.84 (30 min)
Prolactin (ng/mL)	6.1-30.5	20.8	53.9 (30 min)
Luteinizing hormone (mIU/mL)	0.8-5.7	23.2	52.6 (90 min)
Follicle-stimulating hormone (mIU/mL)	2.0-8.3	49.8	62.1 (120 min)

Blood samples were collected in the morning before (basal) and at 15, 30, 60, 90, and 120 min after i.v. administration of the following: 100 µg of CRH, 100 µg of GRF, 500 µg of TRH, and 100 µg of LHRH.

C: Growth hormone-releasing peptide 2 (GHRP-2) stimulation test performed in November 2019.

	Reference range*	Basal	Peak (time at peak)
Growth hormone (ng/mL)	0-2.47	0.4	45.5 (30 min)

Blood samples were collected in the morning before (basal) and at 15, 30, 45, and 60 min after i.v. administration of 100 µg of GHRP-2. *Basal levels.

Figure 1. Magnetic resonance imaging (MRI) of the brain. Plain MRI scans obtained in August 2019 (**A:** T1-weighted image; **C:** T2-weighted image) and in November 2019 (**B:** T1-weighted image; **D:** T2-weighted image) show no abnormalities in the hypothalamus, hypophyseal stalk, or pituitary gland (arrows).

(134 mEq/L) (**Table 3**). In addition, the patient's plasma cortisol level was low (1.4 μg/dL). An electrocardiogram revealed a normal sinus rhythm with no loss of P waves, widening of the QRS complex, or arrhythmia, but tall peak T waves were seen in the precordial leads.

Infusion therapy with normal saline to promote diuresis, sodium bicarbonate for HMA, and glucose/insulin were promptly administered to correct hyperkalemia (**Figure 2**). In addition, the patient began taking corticosteroid replacement therapy with oral hydrocortisone (15 mg/d) immediately after

completing a rapid ACTH stimulation test, which indicated central AI (**Table 2A**). Her anorexia, general weakness, back pain, and muscle pain resolved within a few days and she became ambulatory. Infusion therapy was discontinued after the patient's blood electrolytes (sodium, potassium, and chloride) and pH normalized. She subsequently was administered oral sodium bicarbonate (2 g/d) to treat her ileal conduit-related chronic HMA.

Dynamic tests for pituitary function revealed low ACTH and cortisol release after the administration of corticotropin-releasing

Table 3. Laboratory findings on admission in November 2019.

Blood chemistry		
Total protein	7.2 g/dL	(6.6-8.1)
Albumin	3.4 g/dL	(4.1-5.1)
Creatine phosphokinase	83 U/L	(41-153)
Urea nitrogen	37.4 mg/dL	(8.0-20.0)
Creatinine	1.79 mg/dL	(0.46-0.79)
Sodium	134 mEq/L	(135-147)
Potassium	6.3 mEq/L	(3.5-4.8)
Chloride	113 mEq/L	(98-108)
C-reactive protein	0.85 mg/dL	(0-0.14)
Casual plasma glucose	119 mg/dL	(70-139)
Endocrinology		
Adrenocorticotropic hormone	16.6 pg/mL	(7.2-63.3)
Cortisol	1.4 µg/dL	(7.1-19.6)

Plasma renin activity	15.7 ng/mL/h	(0.2-2.3)
Aldosterone	12.3 ng/dL	(3.0-15.9)
Arginine vasopressin	0.9 pg/mL	
Thyroid-stimulating hormone	4.80 µIU/mL	(0.50-5.00)
Free thyroxine	1.46 ng/dL	(0.90-1.70)
Free triiodothyronine	2.57 pg/mL	(2.30-4.00)
Venous blood gas analysis		
pH	7.204	
Bicarbonate ion	13.0 mmol/L	
Partial carbon dioxide pressure	34.2 mmHg	
Partial oxygen pressure	37.5 mmHg	
Base excess	-13.6 mmol/L	
Lactic acid	9.0 mg/dL	
Anion gap	9.8 mmol/L	

The reference range for each parameter is shown in parentheses. Blood samples were collected in the morning with the patient in the supine position.
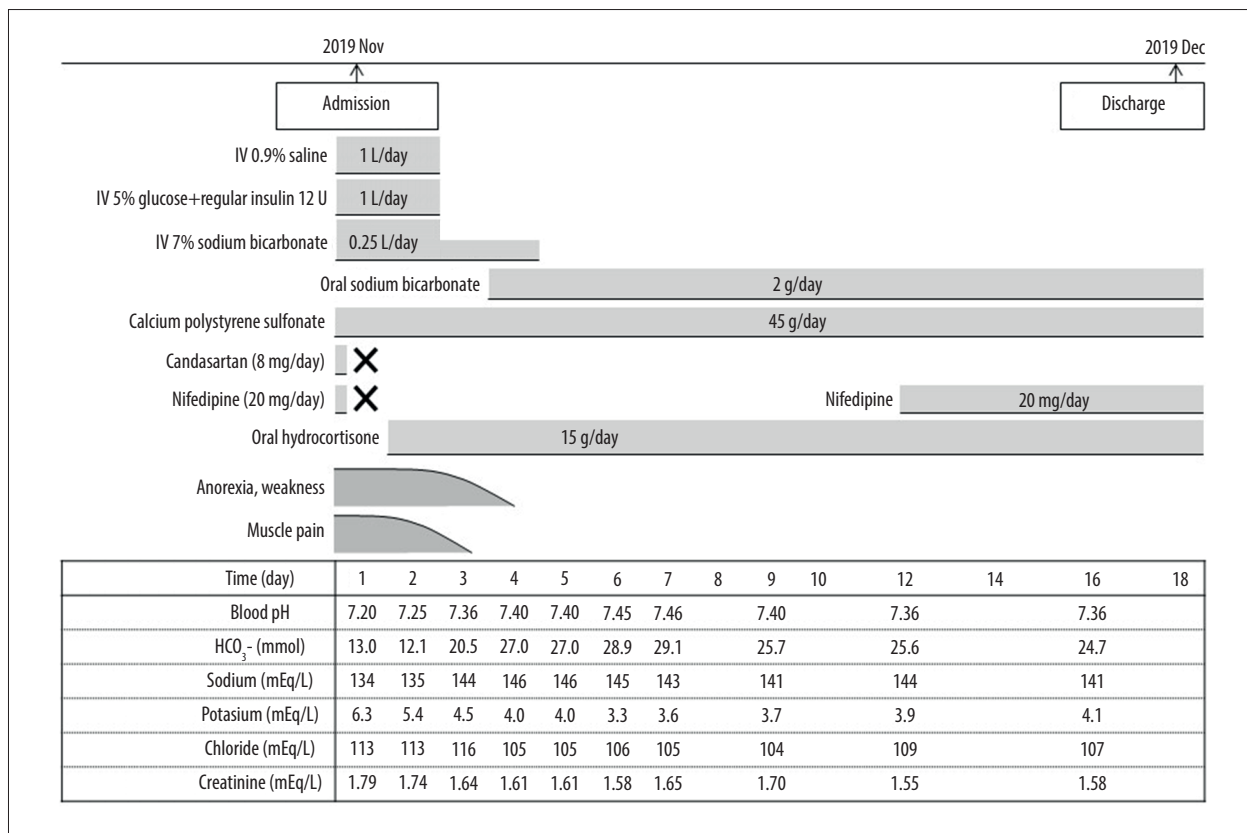

Time (day)	1	2	3	4	5	6	7	8	9	10	12	14	16	18
Blood pH	7.20	7.25	7.36	7.40	7.40	7.45	7.46		7.40		7.36		7.36	
HCO$_3$- (mmol)	13.0	12.1	20.5	27.0	27.0	28.9	29.1		25.7		25.6		24.7	
Sodium (mEq/L)	134	135	144	146	146	145	143		141		144		141	
Potassium (mEq/L)	6.3	5.4	4.5	4.0	4.0	3.3	3.6		3.7		3.9		4.1	
Chloride (mEq/L)	113	113	116	105	105	106	105		104		109		107	
Creatinine (mEq/L)	1.79	1.74	1.64	1.61	1.61	1.58	1.65		1.70		1.55		1.58	

Figure 2. Clinical course of the patient during hospitalization. HCO$_3$ – bicarbonate ion.

Table 4. Summary of reports of patients who exhibited isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) associated with cancer treatment with programmed cell death 1 inhibitors.

Ref.	Age/sex	Target cancer	PD-1 inhibitor administered	Period from drug initiation to IAD onset (months)	Major symptoms at IAD onset	Plasma ACTH (pg/mL)
[6]	50/M	Melanoma	Nivolumab	3.5	Anorexia, fatigue, weakness	4.9
[7]	55/M	Melanoma	Nivolumab	3	Anorexia, nausea, malaise, myalgia	<1.0
[8]	76/F	Melanoma	Nivolumab	6	Fatigue, appetite loss	6.7
[8]	54/M	Poorly differentiated lung carcinoma	Nivolumab	5	Fatigue, nausea	7.0
[8]	64/M	Lung adenocarcinoma	Nivolumab	4.5	Fatigue, appetite loss	<2.0
[8]	57/M	Large cell lung carcinoma	Nivolumab	4.5	Appetite loss, nausea	2.9
[9]	68/M	Melanoma	Nivolumab	7	N.D.	<1.0
[10]	76/F	Melanoma	Nivolumab	5	Anorexia, bradykinesia	7.2
[11]	39/M	Melanoma	Nivolumab	9	General malaise	6.9
[11]	50/F	Melanoma	Nivolumab	10	Fatigue, fever, dizziness	<1.0
[12]	60/M	Non-small cell lung cancer	N.D.*	5	Fatigue, anorexia, exertional dyspnea	6
[12]	72/M	Non-small cell lung cancer	N.D.*	4.5	Fatigue, anorexia, vomiting	<2.0
[12]	71/M	Small cell lung cancer	N.D.*	5	Fatigue, anorexia, nausea	8.5
[13]	75/M	Lung adenocarcinoma	Nivolumab	6	Appetite loss, fatigue	<1.0
[14]	74/M	Renal cell carcinoma	Nivolumab	2.5	Appetite loss, nausea, fatigue	14.4
[15]	60/M	Lung adenocarcinoma	Nivolumab	5	Anorexia, fatigue	1.4
[16]	80/M	Melanoma	Pembrolizumab	10.5	Headache, muscle weakness	<5
[16]	43/F	Melanoma	Nivolumab	7	Asthenia, fever	5
[17]	54/M	Renal cell carcinoma	Nivolumab	6	Consciousness disturbance, fatigue	33.2
[18]	55/M	Pulmonary pleomorphic carcinoma	Nivolumab	8	Asthenia, nausea, hypotension	4
[19]	63/F	Lung adenocarcinoma	Nivolumab	8	Anorexia, fatigue, weakness	3.1
[20]	63/F	Melanoma	Nivolumab	8	Fatigue	<1.0
[21]	58/M	Melanoma	Nivolumab	8	Appetite loss, fatigue, weakness	<2.0
[22]	55/F	Invasive breast ductal carcinoma	Pembrolizumab	14	Chest pain, hypotension	<1.6

Table 4 continued. Summary of reports of patients who exhibited isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) associated with cancer treatment with programmed cell death 1 inhibitors.

Ref.	Age/ sex	Target cancer	PD-1 inhibitor administered	Period from drug initiation to IAD onset (months)	Major symptoms at IAD onset	Plasma ACTH (pg/mL)
[23]	79/M	Squamous cell lung cancer	Nivolumab	7	Nausea, appetite loss, walking difficulty	<1.0
[24]	72/F	Melanoma	Nivolumab	15	General malaise, appetite loss	9.6
[25]	71/M	Renal cell carcinoma	Nivolumab	6	Appetite loss, malaise, consciousness disturbance	4.5
[26]	69/F	Lung adenocarcinoma	Nivolumab	7	Anorexia, fatigue, weakness	2.6
[27]	70/M	Urothelial carcinoma	Nivolumab	4.5	Anorexia, nausea, general weakness	10
[28]	59/M	Non-small cell lung cancer	Pembrolizumab	7	Anorexia, fatigue, slight fever	17.4
[29]	85/F	Squamous cell lung carcinoma	Pembrolizumab	5	Appetite loss, fatigue	8.3
[30]	65/F	Cecal cancer	Pembrolizumab	1.5	Fatigue	3.0
Present case	78/F	Urothelial carcinoma	Pembrolizumab	4.5	Anorexia, general weakness, muscle pain	16.6

Ref.	Plasma cortisol (µg/dL)	Serum sodium (mEq/L)	Serum potassium (mEq/L)	Morphological abnormality of the pituitary evident on MRI	Other IRAEs	Comorbid conditions
[6]	1.7	127	3.9	Mild pituitary enlargement	(–)	(–)
[7]	0.5	N.D.	N.D.	(–)	Interstitial pneumonia, hypothyroidism	(–)
[8]	<1.0	123	N.D.	(–)	(–)	(–)
[8]	<1.0	130	N.D.	(–)	(–)	(–)
[8]	<1.0	127	N.D.	(–)	(–)	(–)
[8]	<1.0	137	N.D.	(–)	(–)	(–)
[9]	<0.8	N.D.	N.D.	(–)	(–)	(–)
[10]	<1.0	123	N.D.	N.D.	(–)	(–)
[11]	0.3	N.D.	N.D.	(–)	(–)	(–)
[11]	<1.0	N.D.	N.D.	(–)	(–)	(–)
[12]	0.6	133	N.D.	(–)	(–)	(–)
[12]	0.3	138	N.D.	(–)	(–)	(–)
[12]	3.2	139	N.D.	(–)	Type 1 diabetes mellitus	(–)
[13]	0.4	133	4.5	(–)	(–)	(–)
[14]	2.3	126	4.3	(–)	(–)	(–)

Table 4 continued. Summary of reports of patients who exhibited isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) associated with cancer treatment with programmed cell death 1 inhibitors.

Ref.	Plasma cortisol (µg/dL)	Serum sodium (mEq/L)	Serum potassium (mEq/L)	Morphological abnormality of the pituitary evident on MRI	Other IRAEs	Comorbid conditions
[15]	1.5	N.D.	N.D.	(−)	Primary hypothyroidism	(−)
[16]	0.4	132	3.6	(−)	Primary hypothyroidism	(−)
[16]	0.8	131	4.5	(−)	Primary hypothyroidism, vitiligo, Type 1 diabetes mellitus	(−)
[17]	3.7	131	4	(−)	Primary hypothyroidism	(−)
[18]	Undetectable	130	Normal	(−)	Type 1 diabetes mellitus	(−)
[19]	1.6	117	3.9	Mild pituitary enlargement	(−)	Primary hypothyroidism caused by prior external irradiation of the neck
[20]	3.5	137	N.D.	(−)	Thyrotoxicosis	(−)
[21]	0.3	136	5.3	(−)	Thyroiditis, hypercalcemia	Kidney dysfunction, T2D, hypertension
[22]	0.9	132	4.3	(−)	Acute pericarditis, primary hypothyroidism	(−)
[23]	0.2	129	4	(−)	(−)	(−)
[24]	Undetectable	120-127	N.D.	(−)	Primary hypothyroidism	(−)
[25]	0.1	122	3.8	(−)	(−)	Hypertension, primary hypothyroidism
[26]	<0.2	124	4.8	Mild pituitary atrophy	Primary hypothyroidism	(−)
[27]	1.4	120	N.D.	(−)	Guillain-Barré syndrome	Hypertension, nephroangiosclerosis
[28]	0.9	137	N.D.	(−)	Primary hypothyroidism	(−)
[29]	0.9	122	N.D.	(−)	(−)	(−)
[30]	0.5	N. D.	N.D.	(−)	(−)	(−)
Present case	1.4	134	6.3	(−)	(−)	HMA due to ileal conduit, CKD, T2D, hypertension

ACTH – adrenocorticotropic hormone; CKD – chronic kidney disease; HMA – hyperchloremic metabolic acidosis; IRAE – immune-related adverse event; MRI – magnetic resonance imaging; N.D. – not determined; T2D – type 2 diabetes mellitus. * Nivolumab or pembrolizumab.

hormone (CRH) (**Table 2B, 2C**); secretory reserves of thyroid-stimulating hormone, growth hormone, prolactin, follicle-stimulating hormone, and luteinizing hormone were normal for the patient's age. These findings indicated IAD.

Brain MRI revealed no abnormality and excluded metastatic involvement of the pituitary gland, but not anti-PD-1-related hypophysitis (**Figure 1B, 1D**). Abdominal CT detected no abnormality (thus, no calcification or metastasis) in the adrenal glands.

Because the patient had not been exposed to other possible triggers of hypopituitarism with central AI, such as head trauma, pituitary surgery, or radiotherapy [34], and she had not received exogenous steroids during pembrolizumab therapy, she was diagnosed with IAD attributable to pembrolizumab-related hypophysitis.

The patient continued on oral hydrocortisone (15 mg/d), sodium bicarbonate (2 g/d), and calcium polystyrene sulfonate (30 g/d) and was discharged 18 days after admission. Her clinical course since then has been uneventful for more than 6 months.

Discussion

Table 4 summarizes the characteristics of the reported cases of anti-PD-1-related IAD [6-30]. Patients with different types of cancer developed IAD with symptoms of cortisol deficiency, such as anorexia, fatigue, and general weakness. The time between drug initiation and the development of IAD ranged from 1.5 to 15 months. Many patients presented with hyponatremia but their serum potassium levels were normal. In the present case, the patient developed IAD 4 1/2 months after initiation of a drug to treat advanced ureteral cancer and had severe hyperkalemia.

Hyperkalemia is a life-threatening electrolyte disturbance that causes muscle weakness, muscle pain, paralysis, and fatal cardiac arrhythmias [35]. Hyperkalemia is a common symptom of primary AI, which is associated with defective mineralocorticoid action due to cortisol and aldosterone deficiencies [33]. In contrast, hyperkalemia is less frequent in patients with central AI because a lack of ACTH does not cause an aldosterone deficiency and mineralocorticoid action is preserved [4,36]. To our knowledge, ours is the first reported case of anti-PD-1-related IAD presenting with severe hyperkalemia.

Potassium is a major intracellular cation. Hyperkalemia can result from disturbed cellular uptake of potassium, due to acidosis, impaired insulin action, or decreased β2 adrenergic activity, as well as disturbed renal excretion of potassium [35]. Disrupted potassium excretion can be due to kidney dysfunction or defective mineralocorticoid action. Certain medications,

such as renin-angiotensin-aldosterone system (RAAS) inhibitors, also induce hyperkalemia, particularly in patients with kidney dysfunction. Although the precise mechanism remains unknown, ICIs cause hyperkalemia on rare occasions, regardless of endocrinopathies [37]. In the present case, cortisol deficiency together with ileal conduit-related HMA (loss of HCO_3 and gain of chloride from the conduit) [32], CKD, T2D, and the use of a RAAS inhibitor probably led to the severe hyperkalemia. Prompt administration of corticosteroids and treatment with normal saline, sodium bicarbonate, glucose/insulin, and cation exchange resin, as well as discontinuation of the RAAS inhibitor, helped the patient recover from severe hyperkalemia (**Figure 2**).

Predisposing factors for pituitary IRAEs are not well known. However, studies have suggested associations between certain human leucocyte antigen haplotypes, such as HLA-DR15, and the development of ICI-related hypopituitarism with secondary AI [38]. Several laboratory abnormalities, such as eosinophilia [12] and hyponatremia [8], also can precede ICI-related secondary AI. Cases have been reported of ICI-related IAD developing after transient elevations in plasma ACTH and cortisol levels [39,40]. In addition, a patient with pembrolizumab-related IAD associated with gradually deteriorating pituitary and adrenal functions has been described; a CRH stimulation test performed 4 months before IAD onset showed a mild reduction in plasma ACTH and cortisol release [28]. In the present case, the patient exhibited transient reductions in plasma ACTH and cortisol levels 3 months before the development of IAD (**Tables 1, 2A**). Subsequently, her blood eosinophils and ACTH levels gradually increased. These findings suggest, in our case, that the transient reductions in ACTH and cortisol levels were probably related to anti-PD-1-related hypophysitis and the consequent IAD.

Conclusions

We have described a patient with pembrolizumab-related IAD who presented with severe hyperkalemia. The present case demonstrates the need for physicians to be aware of severe hyperkalemia as a life-threatening complication of secondary AI induced by ICIs, particularly in patients with predisposing factors, such as kidney dysfunction, T2DM, an ileal conduit, and RAAS inhibitor use.

Acknowledgments

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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