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

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
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, fatigue, and general weakness. In a few days, she had difficulty walking and was admitted to our hospital.

In August 2019, 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 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 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 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 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 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 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 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 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 the left lower part of the ureter. 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. She was diagnosed with type 2 diabetes mellitus (T2D), hypertension, and cerebral infarction. She had no history of smoking or alcohol consumption. She had been prescribed metformin, which effectively controlled her blood glucose, 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 the left lower part of the 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 (HCO3-) 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.

|                      | 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).

|                      | 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, 45, and 60 min after i.v. administration of 100 μg of GHRP-2. *Basal levels.

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

|                      | 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.
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 factor. This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).
Table 3. Laboratory findings on admission in November 2019.

| Blood chemistry | Value          | Reference Range |
|-----------------|----------------|-----------------|
| 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 | Value          | Reference Range |
|---------------|----------------|-----------------|
| Adrenocorticotropic hormone | 16.6 pg/mL | (7.2-63.3) |
| Cortisol      | 1.4 μg/dL      | (7.1-19.6)      |

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

Table 3. Laboratory findings on admission in November 2019.

| Blood chemistry                          | Value          | Reference Range |
|------------------------------------------|----------------|-----------------|
| Total protein                            | 7.2 g/dL       | (6.6-8.1)       |
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| 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                            | Value          | Reference Range |
|------------------------------------------|----------------|-----------------|
| Adrenocorticotropic hormone              | 16.6 pg/mL     | (7.2-63.3)      |
| Cortisol                                 | 1.4 μg/dL      | (7.1-19.6)      |

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

Figure 2. Clinical course of the patient during hospitalization. HCO₃⁻ bicarbonate ion.
| 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. Summary of reports of patients who exhibited isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) associated with cancer treatment with programmed cell death 1 inhibitors.
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.                    | (-) (-) (-)                                   | (-)       | (-)                 |
| [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.                    | (-) (-) (-)                                   | (-)       | (-)                 |
| [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.
Disrupted potassium excretion can be due to kidney dysfunction, as well as disturbed renal excretion of potassium [35].

Hyperkalemia can result from impaired kidney function, such as kidney dysfunction, T2DM, an ileal conduit, 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 Al [38]. Several laboratory abnormalities, such as eosinophilia [12] and hyponatremia [8], also can precede ICI-related secondary Al. 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 Al induced by ICIs, particularly in patients with predisposing factors, such as kidney dysfunction, T2DM, an ileal conduit, and RAAS inhibitor use.

Acknowledgments

The authors thank the clinical laboratory technicians at Uonuma Kikan Hospital for their technical support.
