A Case of Lung Adenocarcinoma with Long-Term Response after Late-Onset Pembrolizumab-Induced Acute Adrenal Insufficiency

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Abstract
Pembrolizumab is an anti-programmed cell death protein-1 antibody that is mainly used for the treatment of non-small cell lung cancer (NSCLC). Immune-related adverse events can be caused by immune checkpoint inhibitors; however, few case reports evaluate the prognosis of patients with NSCLC with late-onset immune-related adverse events. In this case, a 63-year-old man with stage IVA lung adenocarcinoma received pembrolizumab as first-line therapy and achieved a complete response. The patient developed hypothyroidism and skin toxicity owing to pembrolizumab over the course of treatment; however, the patient continued with pembrolizumab. The patient discontinued pembrolizumab after 20 cycles owing to appetite loss from 14 months after the initiation of pembrolizumab. Two months later, the symptoms worsened and the patient was taken to hospital by an ambulance owing to movement difficulty. The patient was diagnosed with acute adrenal insufficiency by endocrinological examinations. The condition of the patient improved after hydrocortisone treatment. Sixteen months have passed without the readministration of pembrolizumab and no recurrence of lung adenocarcinoma has been observed. Late-onset, severe, and diverse immune-related adverse events may be a favorable prognostic factor associated with survival.
Introduction

Pembrolizumab is an anti-programmed cell death protein-1 (anti-PD-1) antibody that is mainly used for the treatment of non-small cell lung cancer (NSCLC). The efficacy and safety of pembrolizumab have been reported in several studies [1–3]. Immune-related adverse events (irAEs), such as pneumonitis, skin toxicities, colitis, thyroid dysfunction, and hepatitis, are caused by immune checkpoint inhibitors (ICIs) and occur in various parts of the body [4]. Adrenal insufficiency is an uncommon irAE and is reported to occur in 0.5% of patients with NSCLC who are treated with anti-PD-1 antibodies [5]. The symptoms of adrenal insufficiency are nonspecific, such as appetite loss, nausea, fever, and apathy [6]. A delay in diagnosis may result in the development of severe symptoms. IrAEs may be a useful favorable prognostic factor associated with survival in patients with NSCLC who are treated with ICIs [7]. Additionally, Hosoya et al. [8] reported that the early development of irAEs in patients who received an ICI is associated with a better clinical outcome.

However, few case reports have evaluated the prognosis of patients with NSCLC with late-onset irAEs. Here, we report on a patient with advanced lung adenocarcinoma who maintained a complete response (CR) after late-onset pembrolizumab-induced acute adrenal insufficiency.

Case Presentation

A 63-year-old man was diagnosed with clinical T1cN3M1b stage IVA lung adenocarcinoma (according to the 8th edition of the TNM Classification of Malignant Tumors). There was a metastatic lesion on the left adrenal gland. After examination of the biopsy tissue, epidermal growth factor receptor mutations, anaplastic lymphoma kinase translocations, and c-ros oncogene 1 translocations were not present, and the programmed cell death protein-ligand 1 (PD-L1) tumor proportion score was 100%. Thus, pembrolizumab monotherapy was used as first-line treatment.

After 9 cycles of 200 mg of pembrolizumab every 3 weeks, the patient achieved a CR (Fig. 1). After 15 cycles of pembrolizumab (from day 319 after the initiation of pembrolizumab), the patient developed skin toxicity (grade 2), but the rash improved after treatment with a steroidal anti-inflammatory agent. After 17 cycles of pembrolizumab (day 369), the patient developed hypothyroidism (grade 2) and commenced 25 μg of levothyroxine daily. The thyroid-stimulating hormone level was 17.98 µIU/mL, the free T3 level was 2.98 pg/mL, and the free T4 level was 0.61 ng/dL. On day 434, the dose of levothyroxine was increased to 100 μg daily, adjusting for the thyroid-stimulating hormone level.

After 20 cycles of pembrolizumab (day 434), anorexia occurred and did not improve. Therefore, pembrolizumab was discontinued. However, the condition of the patient did not improve and the patient gradually became malaise. On day 441, no abnormality was observed in the pituitary gland using magnetic resonance imaging.

On day 484, the patient was taken to the hospital in an ambulance owing to movement difficulty. Physical examination upon admission revealed consciousness at E4V5M6, a body temperature of 39.1°C, blood pressure of 126/76 mm Hg, regular pulse of 120 beats/min, respiratory rate of 12 breaths/min, and arterial blood oxygen saturation of 93% (nasal 1 L/min). The body weight was 11.2 kg lower than that at the initiation of pembrolizumab (from 70 to 58.8 kg). The laboratory findings are shown in Table 1. A blood analysis revealed an elevated inflammatory response: white blood cells at 13,220/µL, C-reactive protein at 9.97 mg/dL, hyponatremia (sodium concentration: 132 mEq/L), hypoglycemia (sugar concentration: 48 mg/dL), an elevated creatinine (Cre) level (1.11 mg/dL), and an elevated creat-
Table 1. Laboratory findings

| Hematology          | Chloride        | 99 mEq/l |
|---------------------|-----------------|----------|
| White blood cells   | Calcium         | 9.7 mg/dL|
| Neutrophils         | C-reactive protein | 9.97 mg/dL |
| Lymphocytes         | Glucose         | 48 mg/dL |
| Monocytes           | Procalcitonin   | 3.83 ng/dL|
| Eosinophils         | Arterial blood gas (nasal 1 L/min) |
| Basophils           | pH              | 7.493    |
| Red blood cells     | PaO₂             | 111 Torr |
| Hemoglobin          | PaCO₂            | 28.4 Torr|
| Hematocrit          | CO₃⁻            | 21.5 mmol/L|
| Platelets           |                  |          |

**Blood chemistry**

| Total protein       | 6.9 g/dL         |
| Albumin             | 3.9 g/dL         |
| Urea nitrogen       | 21.3 mg/dL       |
| Creatinine          | 1.11 mg/dL       |
| Uric acid           | 5.3 mg/dL        |
| Aspartate aminotransferase | 50 U/L        |
| Lactate dehydrogenase | 291 U/L      |
| Creatinine kinase   | 440 U/L          |
| Sodium              | 132 mEq/L        |
| Potassium           | 6 mEq/L          |

| Arterial blood gas (nasal 1 L/min) |
| pH                                | 7.493 |
| PaO₂                              | 111 Torr |
| PaCO₂                             | 28.4 Torr |
| CO₃⁻                              | 21.5 mmol/L |

**Urinalysis**

Gravity 1.020
Protein (-)
Occult blood (-)

**Endocrinology**

Thyroid-stimulating hormone 20.35 µU/mL (0.5–5.0)
Free triiodothyronine 3.02 pg/mL (2.3–4.0)
Free thyroxine 1.46 ng/dL (0.9–1.7)
Adrenocorticotropic hormone 1.1 µg/mL (7.2–63.3)
Cortisol 3.8 µg/dL (5.0–15.0)

Fig. 1. Chest computed tomography scans. **A–C** Performed before the initiation of pembrolizumab. **D–F** Performed on day 196 (after 9 cycles of pembrolizumab) after the initiation of pembrolizumab. **A** A 2.2-cm tumor in the lower lobe of the left lung was seen (red circle). The primary lesion was observed. **B** Mediastinal lymph node metastasis was observed. **C** Left adrenal metastasis was observed. **D**, **E** The size of the primary lesion and mediastinal lymph node was reduced. **F** The left adrenal metastasis had disappeared.
inine kinase (CK) level (440 U/L). A chest X-ray did not reveal any abnormalities. Therefore, the patient was diagnosed with dehydration owing to some infectious disease and fluid replacement and antibiotic treatment was commenced on hospitalization.

On day 2 after admission, a blood analysis revealed that the Cre level (1.74 mg/dL), CK level (5,054 U/L), and hyponatremia (sodium concentration: 128 mEq/L) were further exacerbated. Additionally, blood pressure had lowered to 65/50 mm Hg. On endocrine examination, low levels of cortisol and adrenocorticotropic hormone were revealed (3.8 μg/dL and 1.1 pg/mL, respectively). The patient was diagnosed with acute adrenal insufficiency (grade 4) with prerenal failure induced by pembrolizumab. Hydrocortisone (200 mg daily) and noradrenaline were added to the treatment. The clinical course is shown in Figure 2. On day 5 after admission, the patient experienced an improvement in appetite. Additionally, serum sodium, Cre, and CK levels had improved to within the normal range. On day 8 after admission, the dose of hydrocortisone was reduced to 30 mg daily (orally). The patient was discharged on day 21 after admission because there was no relapse of symptoms after a reduction of oral hydrocortisone to 20 mg daily.

With regard to the subsequent clinical course of the patient, pembrolizumab has been discontinued and the administration of oral hydrocortisone (reduced to 15 mg daily on day 733) has continued without relapse of adrenal insufficiency. On day 984, a chest computed tomography scan showed no recurrence of lung adenocarcinoma, and the patient is being monitored without treatment (Fig. 3).

**Discussion**

Adrenal insufficiency is a rare adverse event induced by anti-PD-1 antibodies [9]. A previous study reported that the median time for the development of adrenal insufficiency is 5.9 months (range 3.2–12.6) and 4 of 10 patients experience another irAE [10]. The latest-onset adrenal insufficiency in a previous case report occurred at 15 months [11]. With regard to the treatment of adrenal insufficiency, corticosteroid replacement therapy is useful and should be administered immediately.
In our case, as the patient had experienced appetite loss 2 months before the onset of adrenal insufficiency, adrenal insufficiency might have developed 14 months after the initiation of pembrolizumab. Thus, earlier administration of hydrocortisone might have avoided the acute adrenal insufficiency. It is unclear whether the incidence of adrenal insufficiency increased the risk of the development of other irAEs. However, considering a previous report [10] and that this case involved three other irAEs, other irAEs may be a risk factor for the incidence of adrenal insufficiency. A previous phase I trial of patients treated with anti-PD-1 antibodies indicated that high doses of hydrocortisone (3–10 mg/kg) are used to treat adrenal insufficiency [12]. In our case, the initial dose of hydrocortisone was 200 mg daily (3.4 mg/kg) for adrenal insufficiency (grade 4) and the symptoms improved. One week later, the dose was gradually reduced to 30 mg daily (0.5 mg/kg). Thus, in the case of mild adrenal insufficiency (grade 1 or grade 2), initial therapeutic glucocorticoid doses can be lower than previously reported [12].

It is unclear whether corticosteroid therapy for irAEs influences prognosis. Several studies have suggested that the incidence of irAEs is a favorable prognostic factor [7, 13]. Toi et al. [13] reported that the median progression-free survival (PFS) in their “irAE induced by nivolumab monotherapy” group was significantly longer than that in the non-irAE group (12.0 vs. 3.6 months, \( p = 0.013 \)). Additionally, the development of irAEs is a predictive factor for response to nivolumab (odds ratio: 0.11, \( p < 0.001 \)). Ida et al. [10] reported that the median overall survival (OS) of their patients with adrenal insufficiency was favorable at 15.4 months; thus, it may be possible to continue ICI treatment with a corticosteroid. A previous study reported that the median OS in an ICI interruption group owing to irAEs was significantly shorter than that in an ICI continuation group (8.3 vs. 14.5 months, \( p = 0.008 \)) [14]. However, a retrospective study reported that the PFS and OS in ICI retreatment cohorts who achieved a partial response or CR before the first onset of irAEs are not significantly longer than those in ICI discontinuation cohorts [15]. It is still unclear whether the onset, diversity, and severity

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**Fig. 3.** Chest computed tomography scans. **A–C** Performed on day 468 after the initiation of pembrolizumab. **D–F** Performed on day 964 after the initiation of pembrolizumab. There was no recurrence of lung adenocarcinoma, and the patient maintained a complete response.
of irAEs is associated with PFS and OS, and which cases continue to benefit from the anti-PD-1 antibody without retreatment.

In our case, the patient has not been retreated with pembrolizumab, in consultation with the patient, because a CR was achieved. Patients who have achieved or nearly achieved a CR after anti-PD-1 antibody treatment when a late-onset and severe irAE develops may continue to benefit from the anti-PD-1 antibody without retreatment.

In conclusion, we presented a patient with NSCLC with a long-term response after late-onset pembrolizumab-induced acute adrenal insufficiency. This case suggests that the occurrence of late-onset, severe, and diverse irAEs may be associated with the sustained efficacy of an anti-PD-1 antibody; thus, an irAE may be a favorable prognostic factor associated with survival.

**Statement of Ethics**

The study was conducted in accordance with the principles of the Declaration of Helsinki. The authors declare that the subject has given his informed written consent to publish his case (including publication of images).

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

K.S. and K.T. wrote the manuscript; K.S., K.T., T.H., T.A., Y.I., R.M., and M.H. collected and analyzed the data; K.T. reviewed the paper.

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