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Case Report

A Case of Isolated Adrenocorticotropic Hormone Deficiency Caused by Pembrolizumab

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Keywords

Anti-programmed cell death 1-specific monoclonal antibody · Microsatellite instability-high cancer · Immune-related adverse events · Isolated adrenocorticotropic hormone deficiency

Abstract

Pembrolizumab (Keytruda®) is an anti-programmed cell death 1-specific monoclonal antibody that has become the standard second-line chemotherapy for unresectable advanced microsatellite instability-high colorectal cancer. Several immune-related adverse events (irAEs), particularly endocrinopathy, are linked to the administration of pembrolizumab. We report here a case of pembrolizumab-induced isolated adrenocorticotropic hormone deficiency in a patient with metastatic colon cancer. A 65-year-old woman visited our hospital for complaints of fatigue with a recent history of primary resection of cecal mucinous cancer and hepatectomy for liver metastasis 3 years ago. Peritoneal dissemination was detected 2 years after surgery. Several chemotherapeutic regimens of cytotoxic and molecular targeted drugs were administered; however, the metastases progressed gradually. Pembrolizumab monotherapy was started because of resistance to treatment. After 2 cycles of pembrolizumab, the patient was severely fatigued. Laboratory data demonstrated that the cortisol level was extremely low. All the other values were within the normal range. Magnetic resonance imaging indicated no mass in the pituitary gland. From multiple tolerance tests, we diagnosed isolated adrenocorticotropic hormone deficiency caused by pembrolizumab. The patient's symptoms improved promptly with cortisol treatment. An abdominal contrast-enhanced computed tomography scan after 5 cycles of pembrolizumab demonstrated that the size of the perito-

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neal dissemination remained unchanged. However, her serum level of carcinoembryonic antigen had decreased to normal levels. Endocrine disorders are very rarely seen as irAEs. Careful laboratory data follow-up is required to inhibit the progression of severe endocrine disorders.

Introduction

Conventionally, the treatment of unresectable advanced colorectal carcinoma is systemic chemotherapy. Immune checkpoint inhibitors (ICIs) are now recognized as a treatment option. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) are the first well-recognized checkpoints that negatively regulate T-cell immune responses [1, 2]. The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®), a PD-1 inhibitor, for patients with unresectable or metastatic solid tumors positive for microsatellite instability (MSI)-high or DNA mismatch repair-deficient biomarkers [3].

This is the first example of an FDA approval of a treatment based on a tumor biomarker and not the type of tumor. Pembrolizumab has shown antitumor activity in a variety of tumors such as non-small cell lung carcinoma, renal carcinoma, urothelial carcinoma, Hodgkin's lymphoma, head and neck carcinoma, and mismatch repair-deficient colorectal carcinoma [4–8]. ICIs have shown autoimmune and inflammatory effects due to increased T-cell activation, which are defined as immune-related adverse events (irAEs) [9–11]. Pembrolizumab has become a mainstay in the treatment for unresectable and advanced MSI-high colorectal carcinoma. Therefore, the frequency with which irAEs will be experienced is also likely to increase. Various organ measurements reveal that organs such as the gastrointestinal tract, endocrine glands, skin, and liver are influenced by ICIs [12].

The incidence of endocrine disorders is low for anti-PD-1 monotherapy [13]. In addition, cases of isolated adrenocorticotropic hormone deficiency are very rare. We present a case of isolated adrenocorticotropic hormone deficiency caused by pembrolizumab in a patient with peritoneal dissemination of mucinous adenocarcinoma of the cecum.

Case Report

A 65-year-old Japanese woman had previously undergone multiple treatments for metastatic cecal cancer. Her original lesion was discovered 3 years earlier when she had laparoscopic ileocecal resection with D3 lymph node dissection for the primary site. After surgery, adjuvant chemotherapy with CAPOX (capecitabine/oxaliplatin) was administered because of the final stage III diagnosis. Abdominal contrast-enhanced computed tomography (CT) after 3 months detected a solitary liver metastasis despite the adjuvant chemotherapy; hence, she had laparoscopic partial hepatectomy for liver metastasis. Then, 1.5 years after the hepatectomy, peritoneal metastases were detected by abdominal contrast-enhanced CT (Fig. 1).

Therefore, several lines of chemotherapy with anti-vascular endothelial growth factor antibody were administered for 1 year. However, as her disease progressed despite these treatments (Fig. 2), she was started on pembrolizumab at 200 mg because the primary resected specimen revealed that the tumor was MSI-high. After 2 cycles of pembrolizumab, the patient experienced severe fatigue. She had no other complaints such as nausea, anorexia, or abdominal pain. Laboratory data showed a decrease in cortisol (0.5 μg/dL) and adrenocorticotrophic hormone (ACTH) levels (3.0 pg/mL). Although the patient did not show any signs

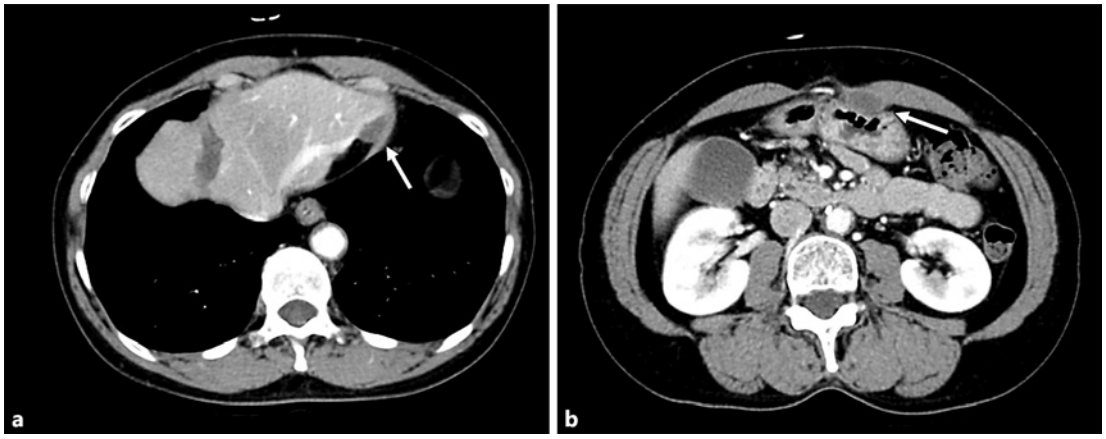

Fig. 1. a, **b** Abdominal contrast-enhanced CT findings before chemotherapy with cytotoxic and molecular targeted drugs. Low-density areas (white arrows) suspected of being peritoneal dissemination were detected.

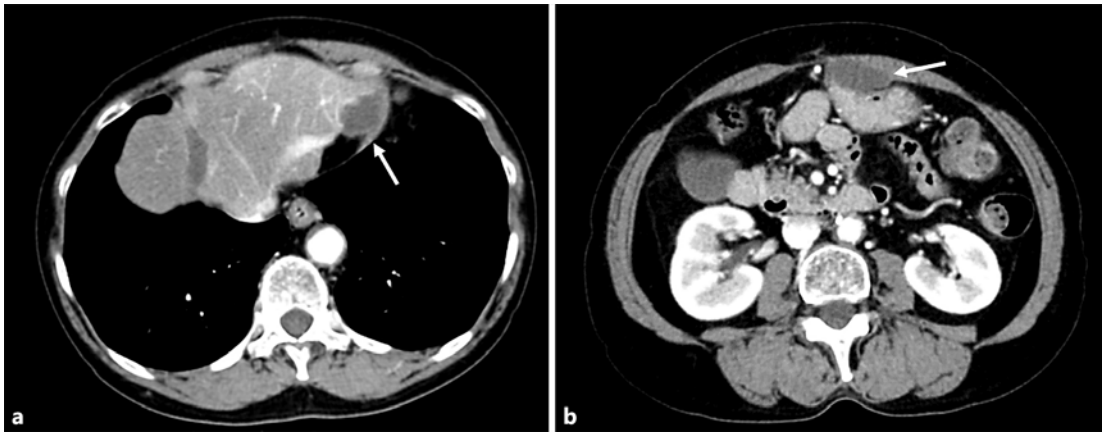

Fig. 2. a, **b** Abdominal contrast-enhanced CT findings after 5 cycles of chemotherapy with cytotoxic and molecular targeted drugs. The size of peritoneal dissemination (white arrows) had increased.

of anemia and neutropenia, additional examinations were performed during hospitalization due to suspected irAEs. She was suspected with having secondary adrenal insufficiency because of basal blood test findings including low ACTH and cortisol levels.

The magnetic resonance imaging (MRI) findings revealed no remarkable findings in the pituitary gland or hypothalamus (Fig. 3). An anterior pituitary function test by combined intravenous administration of the four hypothalamic releasing hormones showed that the levels were within the normal range, except for the corticotropin-releasing hormone load. ACTH and cortisol showed no response to corticotropin-releasing hormone loading, while the insulin tolerance test demonstrated not only ACTH hyposecretion but also a normal reaction of the growth hormone. The patient was diagnosed with an isolated adrenocorticotropic hormone deficiency. An irAE induced by pembrolizumab was the most likely cause of this condition. The patient started hydrocortisone therapy, which immediately relieved her fatigue. She was discharged on the thirteenth day after admission as her fatigue was reduced.

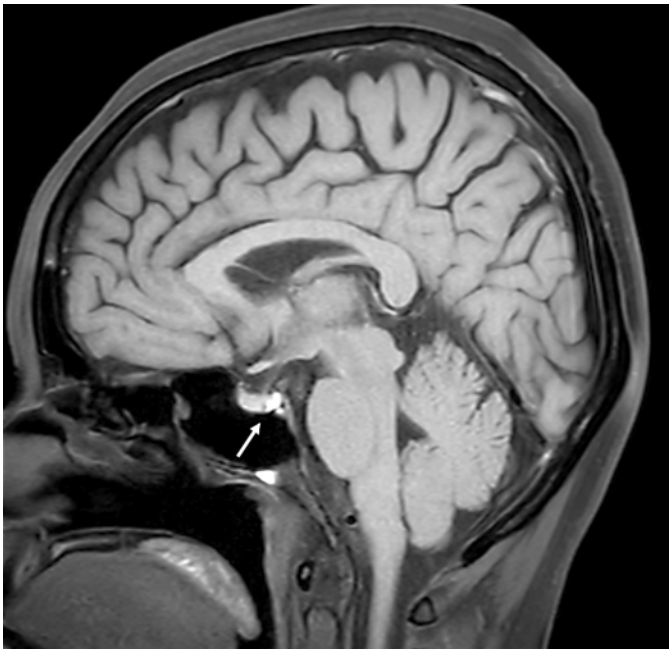

Fig. 3. Head MRI findings. There was no tumor in the pituitary gland (white arrow).

After 5 cycles of pembrolizumab, carcinoembryonic antigen levels were within the normal range, and CT showed that the size of the peritoneal dissemination had progressed slightly (Fig. 4). Pembrolizumab therapy for peritoneal dissemination is still ongoing at the outpatient clinic without relapse of fatigue.

Discussion

Usually, irAEs develop within a few weeks to months after the first administration of ICIs. Up to 29% of patients who have been treated with ICIs show signs of an endocrine disorder [14], which tends to occur after the sixth or seventh week, with a median time to onset of 7–20 weeks [15]. Although the likelihood of irAEs is higher in some patients with autoimmune disease, organ or hematopoietic stem cell transplants, chronic viral infection, organ dysfunction, or advanced age, the influences of these conditions remain controversial [16]. However, adrenal insufficiency was found to be very rare. According to past reports, the incidence of adrenal insufficiency was <4.3% [17, 18]. Some case reports have demonstrated adrenal insufficiency caused by nivolumab treatment. However, we could only find 3 previous case reports on adrenal insufficiency during treatment with pembrolizumab. The following search terms were used in PubMed and Google Scholar: "pembrolizumab and adrenal insufficiency." One case was breast cancer treated with pembrolizumab as neoadjuvant chemotherapy [19]. The other cases were stage IV lung cancer treated with pembrolizumab as systemic chemotherapy [20, 21]. There are no case reports showing isolated adrenocorticotropic hormone deficiency caused by pembrolizumab.

Adrenal insufficiency presents with nonspecific symptoms such as nausea, vomiting, weakness, fatigue, anorexia, abdominal pain, hypotension, fever, headache, and weight loss. Fatigue, especially, is the most common symptom reported by 16–24% of patients who were treated with an anti-PD-1-specific monoclonal antibody [13, 22–24]. Careful follow-up is required because of the relationships between dose and irAEs that have been demonstrated

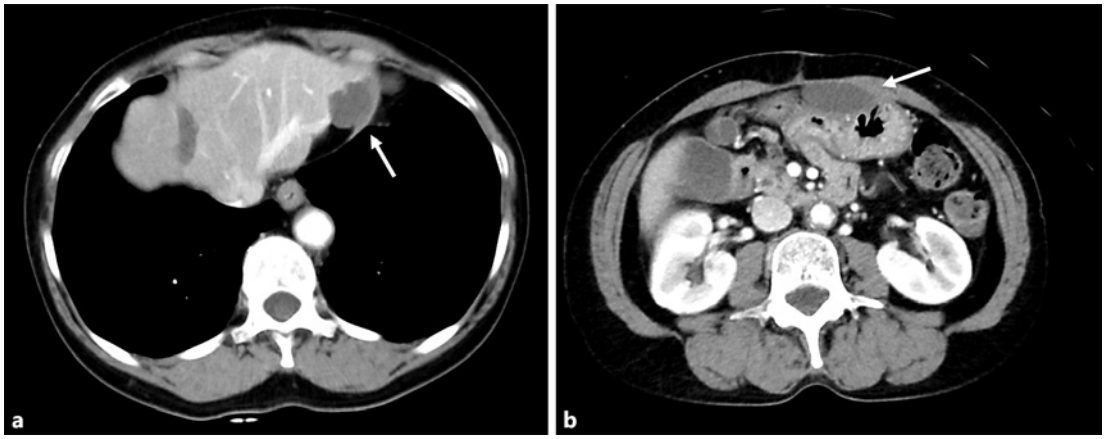

Fig. 4. a, **b** Abdominal contrast-enhanced CT findings after 5 cycles of chemotherapy with pembrolizumab. The size of peritoneal dissemination (white arrows) was unchanged.

for CTLA-4, whereas toxicities of PD-1 antibodies are reported to be independent of dose [25–27]. In our case study, the onset of fatigue from the first administration was 7 weeks, occurring after only 2 cycles of pembrolizumab. Early diagnosis and starting treatment of irAEs are important to prevent life-threatening complications such as an adrenal crisis [28, 29].

If adrenal insufficiency due to ICIs is suspected, it is important to confirm serum cortisol, ACTH, aldosterone, and renin levels. Adrenal insufficiency should be suspected when early morning serum cortisol levels are <3 μg/dL [30]. Adrenal insufficiency can be classified into two types, primary and secondary. The main differential diagnosis of primary adrenal insufficiency is the appearance of brain metastasis during the treatment of colorectal cancers. MRI with gadolinium contrast is very useful to diagnose the brain metastasis [31]. Other hormone levels – for example, thyroid-stimulating hormone, free thyroxine, free tri-iodothyronine, gonadotrophins, and testosterone – should be checked for an accurate diagnosis [10].

Treatment of adrenal insufficiency consists of systemic corticosteroids. Although most irAEs resolve within weeks to months after starting administration of ICIs [12], they may become severe. Thus, an appropriate treatment should be established. As an example, an initial high dose of corticosteroid of 12 mg/kg/day for 3 days could be administered, after which the dose would be reduced gradually over a period of at least 1 month [32]. When irAEs do not improve despite the use of adequate steroid medication, treatment can be supplemented with immunosuppressive medicine such as anti-tumor necrosis factor-α, mycophenolate mofetil, and antithymocyte immunoglobulins [33]. Endocrine-related AEs are irreversible, and it is important to continue administration of corticosteroids to patients who have developed adrenal insufficiency [34, 35]. Longer-term glucocorticoid therapy may lead to additional complications such as cushingoid features, osteoporosis, glaucoma, debilitating proximal muscle weakness, and opportunistic infections [36] including *Aspergillus fumigatus* pneumonia, cytomegalovirus hepatitis, and *Pneumocystis* pneumonia [37–39]. Thus, it is very important for patients being treated with ICIs to be under careful observation.

We could not find any previous reports on isolated adrenocorticotropic hormone deficiency that is caused by pembrolizumab; hence, to the best of our knowledge, this is the first reported case.

Conclusions

We experienced a rare case of isolated adrenocorticotropic hormone deficiency caused by pembrolizumab. One report showed a positive response from ICI-treated patients who have experienced high-grade irAEs [35]. Additionally, accurate diagnosis and starting treatment early are important to prevent the adrenal insufficiency from becoming severe.

Statement of Ethics

The patient consented to the reporting of this case in publication.

Disclosure Statement

We declare no conflicts of interest for this article.

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Author Contributions

T.B., Y.T., K.O., and H.E. wrote the manuscript; Y.T., Y.K., K.O., and M.Y. made the diagnosis and performed treatment. All the authors read and approved the final manuscript.

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