LETTER TO THE EDITOR
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Pharmaceutical Care for Adrenal Crisis Induced by Sintilimab Immunotherapy

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Dear Editor,

Immune checkpoint inhibitors (ICIs) represent a major breakthrough in modern cancer therapy. They regulate the autoimmune response by inhibiting key molecules in the T-cell immunosuppressive pathway, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to exert anti-tumor effects, but they also cause immune-related adverse events (irAEs). Endocrine toxicity is one of the irAEs associated with ICI treatment, among which pituitary inflammation is relatively rare. The incidence of pituitary inflammation induced by PD-1/PD-L1 inhibitors is about 0.4%, and pituitary inflammation complicated with adrenal crisis is even more seldom reported. This condition directly affects or triggers immune cell activity that may lead to impaired pituitary cell function, and once it occurs, it can be life-threatening if not detected and treated in time. PD-1/PD-L1 inhibitor-associated isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) typically presents with nonspecific symptoms like fatigue and is diagnosed by low cortisol, inappropriately normal/low ACTH, and a normal pituitary magnetic resonance imaging (MRI). It represents a predominant form of hypothalamic-pituitary-adrenal axis injury linked to these therapies. Management involves physiological glucocorticoid replacement, not high-dose steroids, allowing most patients to safely continue immunotherapy.

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In this study, we review a case of adrenal crisis in a patient with gastric cancer after receiving sintilimab immunotherapy, and analyze and explore the characteristics of drug-induced adrenal crisis, treatment methods, and precautions needed. The aim is to provide a reference for the rational use of drugs in the clinic, to improve the knowledge of the medical team and pharmacists about the potential complications of immunotherapy, and to provide a better guarantee for the safety and therapeutic efficacy of patients. Through in-depth study of the factors associated with the pathogenesis of pituitary inflammation and adrenal crisis, it is expected to provide new ideas and targets for future immunotherapy strategies.

CASE INFORMATION

A 50-year-old male patient, height 180 cm, weight 66 kg, underwent radical gastrectomy (total gastrectomy) for gastric cancer on October 11, 2017. Postoperative pathology revealed a cardia ulcer type low-differentiated cancer. The patient received postoperative chemotherapy with oxaliplatin and capecitabine. On May 26, 2021, the patient had multiple metastases of the cardia malignant tumor (rTxN3M1) after surgery. Past medical history: 15 years ago, he underwent right nephrectomy because of a “right kidney tumor,” and then he underwent radiotherapy for suspected bone metastasis. Twelve years ago, he underwent radical treatment for right thyroid cancer. Admission diagnoses were as follows: 1) malignant tumor maintenance chemotherapy; 2) esophageal malignant tumor; 3) postoperative cardia; and 4) personal history of thyroid

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malignant tumor.

The patient was currently experiencing malaise and had no other complaints. He was admitted to the hospital for further diagnosis and treatment. Admission examination findings were as follows: temperature, 37.3 °C; blood pressure, 99/61 mm Hg; heart rate, 82 beats/min; respiration, 20 breaths/min; NRS score, 0; and KPS score, 80. Auxiliary examination findings included leukocytes, 4.1×10^9/L; neutrophil percentage, 43.3%; hemoglobin, 84 g/L; platelets, 249×10^9/L; alanine aminotransferase, 34 U/L; glutamine aminotransferase, 58 U/L; blood creatinine, 74 μmol/L; and sodium, 135 mmol/L. The remaining results were normal. The patient's chemotherapy regimen is shown in Table 1.

Treatment: on the first day of admission (December 7, 2021), the patient's spirit was slightly soft, and he had a poor appetite and complained of fatigue, with no other discomfort. On the second day, the patient's fatigue was obvious; he was silent and lazy. At 9:30 AM, his body temperature was 39.8 °C. There were no chills, nausea, vomiting, or other discomforts, and he was given loxoprofen sodium tablets 60 mg orally per doctor's instructions. At 10:10 AM, his body temperature was 39.4 °C, and his blood pressure was 85/43 mm Hg. He was given sodium lactate Ringer injection 500 mL per doctor's instructions for rapid titration. At 11:20 AM, the patient's blood pressure decreased to 67/36 mmHg, and his self-complained fatigue was obvious. His body temperature was 38 °C. He was given norepinephrine 8 mg+5% GS 40 mL to elevate blood pressure, and 8 mL/h to maintain it. Tests for ACTH, serum cortisol, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin (PRL), luteinizing hormone (LH), testosterone, and other parameters were performed.

The laboratory results showed that the patient had an isolated ACTH deficiency, and the patient was considered to be in adrenal crisis due to immune pituitary inflammation caused by sintilimab. Hydrocortisone 100 mg+0.9% NS 100 mL every 8 hours intravenous infusion was given, and the patient's condition improved. After 2 days, his spirit improved, and the hormone was slowly tapered (100 mg every 8 hours for 3 days, 100 mg every 12 hours for 3 days, and 100 mg once daily for 3 days). He was gradually transitioned to oral substitution therapy (hydrocortisone tablets 20 mg in the morning, 10 mg in the evening). The clinical pharmacist recommended blood glucose monitoring during the patient's treatment with hydrocortisone. Norepinephrine was discontinued after 5 days; blood pressure was maintained at 100–110/60–70 mm Hg after discontinuation, and the patient was mentally normal after 7 days. Pituitary MRI revealed no abnormal signs. Coronal and sagittal scans of the pituitary gland showed normal pituitary morphology with a height of about 4.2 mm, and no abnormal occupying foci were seen in the suprasellar cistern, which ruled out pituitary tumors or cerebral metastatic carcinoma. After that, the patient was followed up regularly. The patient took oral hydrocortisone tablets for a long time as replacement therapy, and after 3 months, he had no obvious fatigue, his blood pressure was normal, and there was no other discomfort. However, the serum cortisol and ACTH levels remained low. The patient's serum cortisol and ACTH values are shown in Table 2.

Table 1. Patient chemotherapy regimen.

Treatment cycle	Chemotherapy regimen
Cycle 1 (May 28, 2021)	Paclitaxel (albumin-bound) for injection 400 mg Day 1+sintilimab injection 200 mg Day 1+tegafur/gimeracil/oteracil (Tegio) capsules 60 mg twice a day Day 1–14, every 21 days.
Cycle 2 (June 17, 2021)	Only sintilimab 200 mg Day 1 immunotherapy was given due to poor tolerability.
Cycle 3–5 (July 6, July 27, August 19, 2021)	The original regimen (immuno-combination chemotherapy) was continued for 3 treatments. Chemotherapy was not well tolerated, and malaise was evident.
From Cycle 6 (September 28, October 22, November 14, 2021)	Paclitaxel injection (albumin-bound) was discontinued, and sintilimab injection 200 mg Day 1+tegafur/gimeracil/oteracil (Tegio) capsule 60 mg twice a day Day 1–14, every 21 days was administered.

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Table 2. Serum cortisol and ACTH values after the occurrence of adrenal crisis.

Time	ACTH (reference range, 7.2–63.3), pg/mL	Serum cortisol (reference range, 3.7–19.4 before 10:00 AM and 2.9–17.3 after 5:00 PM), μg/dL
Day 1 (1.67 h) 1:00 PM	<1.0	1.8
Day 1 (5 h) 5:00 PM	<1.0	1.3
Day 2 (21 h) 8:00 AM[a]	<1.0	>59.8
Day 42 8:00 AM	<1.0	3.2
Day 75 8:00 AM	<1.0	0
Day 135 8:00 AM	<1.0	2.3

[a]Hydrocortisone needle shock therapy. ACTH: adrenocorticotropic hormone.

Case Analysis

Referring to the 2022 edition of the gastric cancer diagnosis and treatment guidelines, the clinical pharmacist analyzed the medication regimen of this patient. Capecitabine and oxaliplatin (XELOX) combined with sintilimab was class 1A evidence for positive PD-L1 expression (combined positive score [CPS]≥5) in the first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative advanced gastric cancer. On June 23, 2022, the National Medical Products Administration (NMPA) officially approved sintilimab for the indication of "gastric or gastroesophageal junction adenocarcinoma" without a specific requirement for CPS.

Pituitary inflammation is a common endocrine toxicity of CTLA-4 inhibitors, while the incidence of pituitary inflammation due to PD-1/PD-L1 inhibitor monotherapy is low. A meta-analysis showed that PD-L1 inhibitors caused pituitary inflammation with a probability of <0.1%. Endocrine toxicity associated with ICIs is usually slower to appear, and pituitary inflammation can appear as early as the first day of the treatment period when using CTLA-4 inhibitors (7 to 8 weeks), whereas with anti-PD-1 monotherapy it can appear from weeks 10 to 24. This patient's pituitary inflammation manifested only as ACTH deficiency, known as IAD. It has been shown that the median time to develop IAD after initiation of treatment with ICIs is 6 months (interquartile range [IQR], 4–8).[1] The patient's first use of sintilimab was on May 28, 2021, with 8 consecutive courses of immunotherapy. The last use was on November 14, 2021, and the abnormality was detected upon admission to the hospital on December 8, 2021, approximately 6.5 months after the first use of sintilimab. The clinical pharmacist evaluated the patient using the methods recommended in the Measures for the Reporting and Monitoring of Adverse Drug Reactions and concluded that the association between the drug and the adverse reaction was "probable," making it highly suspicious that the adrenal crisis in this patient was caused by sintilimab (Table 3).

Based on the patient's clinical presentation and laboratory findings, as well as the Common Terminology Criteria for Adverse Events (CTCAE), the patient was diagnosed with immune pituitary inflammation complicated by adrenal crisis (CTCAE grade 4).

Restart of Immunotherapy

After the patient's condition was stabilized, the decision to restart immunotherapy was made under a multi-disciplinary treatment (MDT) discussion in which the clinical pharmacist was also involved. The clinical pharmacist's rationale was given: with reference to the Guidelines for the Management of Toxicity of Immune Checkpoint Inhibitors, for pituitary inflammation presenting with TSH/ACTH and/or gonadotropin deficiency but without symptomatic pituitary enlargement, ICIs can be continued along with alternative endocrine therapy. This patient had IAD, and after clinical symptoms were controlled, a comprehensive evaluation concluded that ICIs could be safely restarted along with alternative endocrine therapy. The goal of this comprehensive treatment regimen is to maximize tumor stability while minimizing discomfort and adverse events for the patient.

The patient's condition was stabilized, and then the immuno-combination therapy with sintilimab was

restarted, while the oral hydrocortisone tablets (20 mg in the morning, 10 mg in the evening) were continued as replacement therapy. The patient did not experience any further associated symptoms of weakness and hypotension during the follow-up period, but the patient's pituitary function was not restored. At the 10-month follow-up, the patient's serum cortisol at 8:00 AM was 0.45 μg/dL, and the ACTH was <1.0 pg/mL. Meanwhile, no tumor progression was observed.

Table 3. Naranjo adverse drug reaction probability scale.

Related questions	Yes	No	Unknown	Patient score	Scoring basis
1. Are there previous conclusive reports on this adverse reaction?	+1	0	0	1	Mentioned in both the drug label and literature reports.
2. Did the adverse reaction appear after the suspected drug was administered?	+2	-1	0	2	The reaction occurred 194 days after the first use of sintilimab.
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1	Symptoms improved after drug withdrawal and symptomatic treatment.
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0	Immunotherapy was restarted along with continued replacement endocrine therapy.
5. Are there alternative causes that could solely have caused the reaction?	-1	+2	0	2	Cannot be reasonably explained by the patient's underlying disease.
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0	Placebo was not used.
7. Was the drug detected in the blood or other fluids in concentrations known to be toxic?	+1	0	0	0	Not measured.
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0	Unknown.
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	Unknown.
10. Was there objective evidence confirming the adverse reaction?	+1	0	0	1	Objective evidence includes patient's serum cortisol, ACTH, thyroid function, and pituitary MRI.
Total score				**7 (Probable)**	

[a]A total score of ⩾9 indicates a definite causal relationship between the drug and the adverse reaction, supported by objective evidence and quantitative assay data. A score of 5–8 indicates a probable causal relationship, supported by objective evidence and quantitative assay data. A score of 1–4 indicates a possible causal relationship, where the association can neither be fully confirmed nor completely ruled out. A total score of ⩽0 indicates a doubtful causal relationship, suggesting that the reaction is coincidental or essentially unrelated. ACTH: adrenocorticotropic hormone; MRI: magnetic resonance imaging.

The clinical pharmacist played a crucial role by titrating the dosage of hydrocortisone based on the patient's clinical response and serum cortisol levels, facilitating a gradual conversion from intravenous to oral administration while avoiding adrenal crisis recurrence. Additionally, the pharmacist monitored for potential drug interactions and provided glycemic management during high-dose glucocorticoid therapy, ensuring the safe continuation of immunotherapy.

Pituitary Immune-Related Adverse Events

The mechanism by which ICIs induce pituitary inflammation is unclear. Sintilimab is a fully human anti-PD-1 antibody, and the antibody-triggered complement pathway, anti-pituitary antibodies (APAs), and human leukocyte antigen (HLA) genotype may be among the causes of pituitary irAEs caused by PD-1 inhibitors.[2] Domestic and international guidelines do not have uniform criteria for the diagnosis of pituitary irAEs, and clinical diagnosis is generally based on patient symptoms, endocrine testing, and MRI examination. However, there are no abnormal manifestations on brain MRI in patients with IAD, making IAD a special form of pituitary irAE,[3] and there is also relevant literature that reports its existence. In contrast to the classic imaging findings of ICI-related

hypophysitis—which frequently presents with pituitary enlargement, heterogeneous enhancement, or stalk thickening on MRI—PD-1/PD-L1 inhibitor-induced IAD is characterized by a notably high frequency of normal pituitary imaging. IAD represents a unique clinicoradiological entity within the spectrum of pituitary irAEs, highlighting the importance of maintaining a high index of suspicion for IAD even in the absence of structural pituitary abnormalities.

The patient had a history of thyroid cancer and nephrectomy. Although current literature lacks definitive evidence establishing pre-existing endocrine organ damage (such as a history of thyroid cancer or nephrectomy) as an independent risk factor for developing ICI-related isolated ACTH deficiency, it is noteworthy that anti-pituitary antibodies have been identified as potential biomarkers for predicting pituitary irAEs.[1] In this context, the patient's history of thyroid cancer might suggest an underlying predisposition to autoimmunity, warranting closer endocrine monitoring during ICI therapy.[4] Pituitary inflammation induced after PD-1/PD-L1 inhibitor treatment often manifests as headache and malaise. In this paper, the patient presented with pituitary irAEs early on, with malaise and poor nadir as the main manifestations, and was poorly tolerated during previous chemotherapy, accompanied by malaise. Cancer-related fatigue (CRF) is one of the most common side effects in patients with malignant tumors, and 96% of the patients who underwent chemotherapy experienced CRF,[5] which is very easy to overlook. A systematic review of 123 cases of ICI-induced IAD reported a median onset time of 6 months (IQR, 4–8 months) after treatment initiation, with fatigue and appetite loss being the most common presenting symptoms.[6] Clinical symptoms of pituitary irAEs are easily relieved, but endocrine recovery is not easily achieved, and failure of the adrenocorticotropic hormone axis is usually permanent, requiring continuous glucocorticoid replacement therapy. In this case, the patient was initially characterized by unrelieved fatigue, malaise, nausea, hyperthermia, and mild hyponatremia. The symptoms improved after treatment with hydrocortisone injection, which was gradually tapered down to the replacement therapy dose, and the patient's serum cortisol and ACTH levels remained unrecovered at a follow-up of 10 months.[7] It has been reported in the literature that pituitary endocrine function is difficult to recover after atezolizumab causing IAD, and ACTH remained low after 24 months of follow-up.

With the widespread use of ICIs, irAEs are becoming more common, especially as rare and new adverse reactions pose new challenges. For example, pituitary inflammation complicated by adrenal crisis is easily overlooked, making routine monitoring of serum cortisol, ACTH, and thyroid function essential. The course of treatment in this case highlights the importance of multidisciplinary collaboration in immunotherapy and the need to integrate individual patient differences when weighing the effectiveness of treatment against the risk of adverse events. Professional decision-making by the healthcare team and ongoing follow-up are essential for the patient's treatment and recovery. In addition, the complexity and challenging nature of endocrine toxic reactions that can occur in the treatment of ICIs are emphasized and need to be carefully managed and monitored.

STATEMENT OF ETHICS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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