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Fluctuations in plasma adrenocorticotropic hormone concentration may predict the onset of immune checkpoint inhibitor-related hypophysitis

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ABSTRACT

Immune checkpoint inhibitor (ICI)-related hypophysitis (RH) is a common immune-related adverse event. The early detection of ICI-RH prevents life-threatening adrenal insufficiency. However, good predictors of secondary adrenal insufficiency in ICI-RH have not yet been reported. We hypothesized that fluctuations in plasma adrenocorticotropic hormone (ACTH) and cortisol levels occur similarly to those in thyroid-stimulating hormone and thyroid hormone (thyroxine and triiodothyronine) levels in ICI-related thyroiditis. Here, we sought to test this hypothesis. Patients who used ICI and had a history of measurement of plasma ACTH and serum cortisol concentrations were retrieved from electronic medical records, and those with a history of glucocorticoid use were excluded from the analysis. We evaluated fluctuations in plasma ACTH and serum cortisol concentrations and the development of ICI-RH. For patients with ICI-RH, data at three points (before ICI administration (pre), maximum ACTH concentration (peak), and onset of ICI-RH) were analyzed to evaluate hormone fluctuations. A total of 202 patients were retrieved from the medical record. Forty-three patients were diagnosed with ICI-RH. Twenty-six out of 43 patients had sufficient data to evaluate fluctuations in plasma ACTH and serum cortisol concentrations and no history of glucocorticoid use. ACTH concentrations changed from 37.4 (29.9–48.3) (pre) to 64.4 (46.5–106.2) (peak) pg/mL (1.72–fold increase, p=0.0026) in the patients with ICI-RH before the onset. There were no differences in cortisol concentrations between the pre and peak values in patients with ICI-RH. We also evaluated the fluctuations in plasma ACTH and serum cortisol levels in patients who did not receive ICI-RH (62 cases). However, elevation of plasma ACTH levels was not observed in patients without ICI-RH, suggesting that transient elevation of plasma ACTH levels is a unique phenomenon in patients with ICI-RH. In conclusion, plasma ACTH levels were transiently elevated in some patients with ICI-RH before the onset of secondary adrenal insufficiency. Monitoring the ACTH levels and their fluctuations may help predict the onset of ICI-RH.

BACKGROUND

Immune checkpoint inhibitors (ICIs) are widely used to treat various malignant neoplasms. Programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are the ICI targets. However, ICI treatment can lead to immune-related adverse events (irAEs), including autoimmune endocrinopathies. Pituitary insufficiency due to ICI-related hypophysitis (ICI-RH) is a common irAE. The development of pituitary insufficiency in patients receiving ICIs is associated with better overall survival in several malignancies.[1] However, the appropriate diagnosis, early detection, and treatment of hypopituitarism are essential. Adrenal insufficiency due to hypopituitarism can be lethal if not properly managed. Life-threatening adrenal insufficiency is characterized by appetite loss, abdominal pain, and extreme fatigue, which mimics sepsis, brain metastasis, and cachexia.[2] The frequency and timing of onset vary with ICI class. The frequency of ICI-RH in anti-CTLA-4 antibody (Ab)-based regimens is 5%–10% with a median onset of 9–12 weeks, and that in anti-programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1)-based regimens is <1% with a median onset of 26 weeks.[3] However, the timing of disease onset varies considerably among cases, hindering the prediction of disease onset.

The clinical features of anti-CTLA-4 and anti-PD-1/anti-PD-L1 Ab-RH differ. Anti-CTLA-4 Ab-RH causes panhypopituitarism, including secondary hypothyroidism, hypogonadotropic hypogonadism, and secondary

adrenal insufficiency.[4] In contrast to anti-CTLA-4 Ab-RH, anti-PD-1/PD-L1 Ab-RH predominantly causes an isolated adrenocorticotropic hormone (ACTH) deficiency.[5] These different patterns may result from different underlying mechanisms.[6] However, secondary adrenal insufficiency accounts for 83% of ICI-RH cases.[7] Therefore, predictive markers for the onset of secondary adrenal insufficiency are essential.

Tahir *et al* reported autoantibodies against guanine nucleotide-binding protein G(olf) subunit alpha (GNAL) and integral membrane protein 2 B (ITM2B) as biomarkers for ICI-RH.[8] However, these biomarkers are still under investigation and cannot be measured routinely. Therefore, markers that can predict the onset of hypopituitarism under regular measures are necessary. Several studies have reported an elevation of the eosinophil fraction and count during the last visit and at the onset of hypopituitarism.[9 10] These studies raised a crucial point; however, one report also showed that the cortisol concentration had already mildly decreased at the last visit, which may be seen as a sign that ICI-RH is already under development.[9] Eosinophilia is a well-known marker of already developed adrenal insufficiency.[11]

Thyroiditis is one of the most common irAEs. ICI-related thyroiditis typically occurs biphasically: thyrotoxicosis, followed by a subsequent persistent hypothyroidism.[12] In the initial thyrotoxicosis phase, free thyroxine and triiodothyronine levels are elevated while those of thyroid-stimulating hormone are suppressed. In the hypothyroidism phase, the pattern is reversed. The underlying mechanism of ICI-related thyroid dysfunction remains unknown. We speculated that, if the pituitary gland is damaged in ICI-RH by a mechanism similar to that of thyroiditis, plasma ACTH and serum cortisol levels, which are indicators of the hypothalamic pituitary adrenal (HPA) axis in routine practice, may fluctuate during the process. If so, they could potentially be used as predictive factors for the onset of secondary adrenal insufficiency in ICI-RH. To explore this possibility, we collected data on plasma ACTH and serum cortisol levels in patients using ICIs and analyzed fluctuations in hormone concentrations.

METHODS

Patients

Participants gave informed consent to use the medical records. To avoid arbitrarily selecting and detecting patients with ICI-RH from the electronic medical records of Kobe University Hospital, we retrieved patient data using the following criteria: (1) use of ICI(s) at least once and 2. measured fasting AM plasma ACTH and serum cortisol levels at least twice. We thought that if ACTH and cortisol concentrations were measured at least twice, we could identify the patients who developed ICI-RH. The data extraction period for starting the ICI treatment was from April 2014 to March 2022. The follow-up period was until October 2023. The reason for the follow-up duration was that 18 months had passed since the initiation of ICI treatment and most ICI-RHs had developed by that time.[13] After retrieval, we checked the patients' medical records and diagnoses of ICI-RH. The diagnosis of ICI-RH was made based on previously reported diagnostic criteria.[14] Since ICI-RH often occurs with ACTH insufficiency, cases with ACTH insufficiency are also evaluated for other pituitary hormones. Some chemotherapy protocols that combine ICI and cytotoxicity require exogenous glucocorticoids as adjuvants to relieve side effects. Exogenous glucocorticoids suppress the HPA axis, challenging the evaluation of the ACTH and cortisol concentrations to correctly diagnose hypopituitarism. Therefore, patients with a history of glucocorticoid use were excluded from our analysis. We also excluded patients who regularly used a pharmacological dose of glucocorticoids for autoimmune or allergic diseases from the ACTH and cortisol concentration analyses for the same reason. Thus, only cases of ICI-related hypopituitarism in which ACTH and cortisol fluctuations could truly be evaluated were selected. Cases in which glucocorticoids made it challenging to assess ACTH and cortisol levels were excluded.

Data collection and analysis

After selecting patients who were truly diagnosed with ICI-RH, we analyzed the ACTH and cortisol concentrations at three points during the clinical course: (1) Just before the initiation of ICI therapy (pre), (2) The timing that showed the maximum ACTH concentration after initiation before the onset of ICI-RH (peak), and (3) The onset of ICI-RH. Therefore, we excluded data that lacked the above-mentioned three points for ACTH and cortisol levels. Data on the Na, K, and eosinophil fractions at the above-mentioned points were also collected. We also analyzed the data of patients who did not develop ICI-RH (non-ICI-RH). ACTH and cortisol concentrations were analyzed at two different time points: (1) Just before the initiation of ICI (pre) and (2) The timing shows the maximum ACTH concentration after initiation of ICI (peak).

Statistical analysis

Statistical analyses were performed using JMP Statistical Database Software V.12·2·0 (SAS Institute). The Mann-Whitney U test and Wilcoxon signed-rank test were performed as appropriate. Statistical significance was set at $p<0.05$.

RESULTS

Using the criteria mentioned above, the electronic medical records of 202 patients who used ICIs at least once and whose plasma ACTH and serum cortisol concentrations were measured at least twice were obtained. Although screening was conducted using the criterion of at least two measurements of ACTH and cortisol levels, all selected patients had at least three measurements. Among them, 43 patients were diagnosed with ICI-RH.

Table 1 Patient characteristics

		ICI-RH cases		Non-ICI-RH cases
No of patients		26		62
Age of ICI therapy initiation		68 (62–71)		70 (65–74)
Sex (male and female)		19 and 7		49 and 13
Primary organ of the tumors*	Kidney	12	Kidney	14
	Lung	6	Lung	15
	Pharynx	4	Pharynx	13
	Skin	2	Skin	5
	Esophagus	2	Esophagus	6
	Stomach	2	Stomach	4
	Uterus	1		
	Unknown primary origin	1	Unknown primary origin	3
			Urinary duct	3
			Bladder	2
			Parotid gland	1
			Liver	1
ICI-related thyroiditis (n, %)		5, 19.2%		13, 20.1%
ICI type†	Nivolumab	15		32
	Pembrolizumab	5		16
	Ipilimumab+nivolumab	5		6
	Atezolizumab	1		5
	Survalumab	0		4

*Includes multiple kinds of tumors.
†One non-ICI-RH case switched nivolumab monotherapy to the combination of ipilimumab and nivolumab after one course.
ICI, immune checkpoint inhibitor; RH, related hypophysitis

All patients in our cohort with ICI-RH had only reduced ACTH and cortisol levels, while the levels of other pituitary hormones were unaffected, resulting in the diagnosis of isolated ACTH deficiency. Isolated ACTH deficiency was diagnosed as previously described.[15] Five patients were excluded owing to a history of glucocorticoid use as an adjuvant. One patient who used pharmacological glucocorticoids to treat allergic diseases was also excluded from the analysis. Eleven patients lacked ACTH or cortisol data just before the initiation of ICI and/or the peak ACTH concentration after initiation, before the onset of ICI-RH. Similarly, for non-ICI-RH cases, we excluded patients who were inappropriate for analysis because of a history of steroid use or lack of data. Finally, we analyzed the fluctuations in ACTH and cortisol concentrations in 26 and 62 patients with ICI-RH and non-ICI-RH, respectively (table 1).

During the clinical course, fluctuations in the ACTH and cortisol concentrations were observed (table 2, figure 1). ACTH concentrations changed from 37.4 (29.9–48.3) (pre) to 64.4 (46.5–106.2) (peak) pg/mL (figure 1A). ACTH concentrations were significantly elevated before ICI-RH onset after initiating ICI therapy (1.72-fold increase, p=0.0026). The time from ICI initiation to peak and from peak to ICI-RH onset was 49 (28–127) and 70 (39–186) days, respectively. There were no correlations between the pre and peak ACTH concentrations. Cortisol concentrations were statically not elevated at the peak of ACTH concentration (pre and peak concentrations were 11.8 (10.4–15.2) (pre) and 14.5 (11.5–16.5) (peak) µg/dL, respectively; p=0.1742) (figure 1B). The change in the ACTH/cortisol ratio was statistically significant (pre and peak ratios were 3.30 (2.17–4.11) (pre) and 4.60 (3.33–7.01) (peak), respectively; p=0.0070) (figure 1C). We analyzed the eosinophil fraction at peak ACTH levels. We collected data on the eosinophil fraction from 22 of 26 patients. The eosinophil fraction at the time of peak ACTH levels was 2.8% (1.4%–5.9%) (reference range: <7%) in this group. Only three patients showed an elevated eosinophil fraction (12.7, 13.0, and 25.0%). Brain MRI findings were obtained from 21 patients; no signs of pituitary enlargement were found in any case.

Considering that the mechanism of pituitary dysfunction may differ between the ACTH-elevated and ACTH-non-elevated groups, we analyzed the clinical data of the groups. Since the median elevation of ACTH was a 1.72-fold increase, we divided the patients into two groups for analysis: the ACTH-increased group at the peak (>1.72) and the non-increased group (<1.72). However, there were no noticeable clinical differences (age; sex; type

Table 2 Fluctuations in ACTH and cortisol levels in patients with or without ICI-RH

	ICI-RH			Non-ICI-RH	
	Pre	Peak	ICI-RH onset	Pre	Peak
ACTH (pg/mL)	37.4 (29.9–48.3)	64.4 (46.5–106.2)*	4.6 (2.8–7.9)*†	31.6 (21.1–37.3)	36.5 (24.3–50.9)
Cortisol (µg/dL)	11.8 (10.4–15.2)	14.5 (11.5–16.5)	0.9 (0.5–4.6)*†	12.7 (10.6–16.0)	14.4 (12.9–18.0)
ACTH/cortisol ratio	3.30 (2.17–4.11)	4.60 (3.44–7.01)*	–	2.30 (1.68–3.23)	2.35 (1.72–3.77)
Serum Na concentration (mEq/L)	139.5 (139.0–141.0)	139.5 (137.3–141.8)	139.0 (137.0–140.0)	140.0 (138.5–141.5)	139.5 (137.5–141.0)
Serum K concentration (mEq/L)	4.2 (3.9–4.4)	4.3 (4.1–4.5)	4.2 (4.1–4.5)	4.3 (4.1–4.5)	4.2 (4.0–4.3)
Eosinophil fraction (%)‡	3.1 (1.5–5.1)	2.8 (1.4–5.9)	4.5 (1.0–9.1)	3.3 (1.0–4.8)	2.9 (1.5–5.3)
Time from ICI initiation to ACTH peak levels (days)	–	49 (28–127)	–	–	77 (39–227)
Time from ACTH peak levels to ICI-RH onset (days)	–	–	70 (39–186)	–	–
Duration of the follow-up from ICI(s) initiation (months)	28.0 (19.5–46.0)			19.0 (10.8–35.5)	

Data are presented as a median (quartile range).
*Statistically different from the pre value (p<0.05).
†Statistically different from the peak value (p<0.05).
‡Data obtained from 22 out of 26 (ICI-RH) and 56 out of 62 (non-ICI-RH) patients.
ACTH, adrenocorticotropic hormone; ICI, immune checkpoint inhibitor; RH, related hypophysitis.

of malignancy; frequency of accompanying thyroiditis; time from ACTH peak to ICI-RH onset; concentrations of ACTH, cortisol, Na, and K; and eosinophil fraction at the onset of ICI-RH) (data not shown). All three patients with elevated eosinophil fractions at peak ACTH levels were included in the non-ACTH-elevated group. The time from ACTH peak levels to ICI-RH onset in these three patients was 18, 39, and 52 days.

Next, differences in fluctuations in ACTH and cortisol levels were evaluated in the non-ICI-RH group (table 2). We collected data on ACTH and cortisol levels at two points: before the initiation of ICI therapy and at the time of highest ACTH concentration during the clinical course. Although no clear ACTH peak existed in the non-ICI-RH cases, as shown in table 2, the maximum ACTH concentrations measured during follow-up were used for analysis, as in the ICI-RH cases (time from the initiation of ICI treatment to the peak was 77 (39–227) days). However, there was no elevation in ACTH, cortisol, or ACTH/cortisol ratio in patients without ICI-RH. We also evaluated the differences in the peak concentrations of ACTH and cortisol, and the ACTH/cortisol ratio between the ICI-RH and non-ICI-RH groups (figure 2). The two groups had no noticeable differences in clinical backgrounds or observation periods. The peak ACTH concentration and ACTH/cortisol ratio, but not the cortisol concentration, of the ICI-RH group were statistically higher than those of the non-ICI-RH group, indicating that fluctuations in ACTH levels are specific to the ICI-RH group.

DISCUSSION

If the pituitary gland is damaged in ICI-RH by a mechanism similar to that of thyroiditis, plasma ACTH and serum cortisol levels should fluctuate during the process and could be used as predictive factors for the onset of secondary adrenal insufficiency in ICI-RH. To explore this possibility, we collected data on plasma ACTH and serum cortisol levels in patients using ICIs and analyzed fluctuations in hormone concentrations. ACTH levels were transiently elevated in patients who developed ICI-RH, and the elevation occurred prior to the onset of ICI-RH. These findings suggest that transiently elevated ACTH levels may be predictive of ICI-RH onset.

Glucocorticoid use suppresses the HPA axis, and ACTH levels are transiently elevated during the recovery of the HPA axis after suspension of chronic corticosteroid therapy.[16] Since glucocorticoid use is common among patients receiving ICIs, only analyses omitting these cases can accurately examine the impact of ICIs on ACTH and cortisol levels as well as ICI-RH. Here, we analyzed patients in whom the effects of glucocorticoid use could be excluded. Hence, although the sample size was small, we could accurately evaluate the effect of ICI on ICI-RH onset and the concentrations of ACTH and cortisol. To

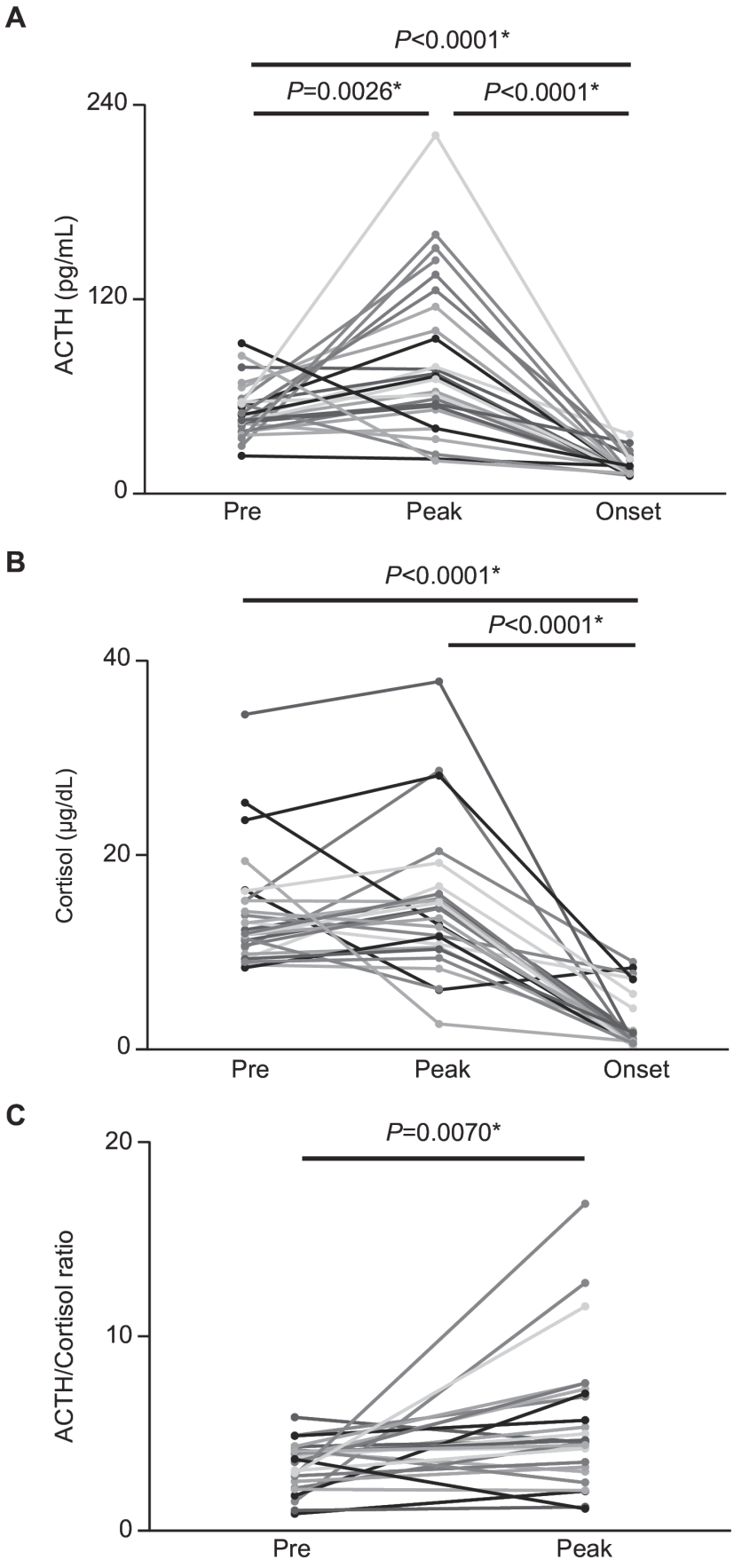

Figure 1 Fluctuations in ACTH and cortisol concentration and ACTH/cortisol ratio in patients with ICI-related hypophysitis (ICI-RH) (n=26). (A) ACTH concentration, (B) Cortisol concentration, and (C) ACTH/cortisol ratio. ACTH, adrenocorticotropic hormone; ICI-RH, immune checkpoint inhibitor-related hypophysitis. (*: *P* <0.05)

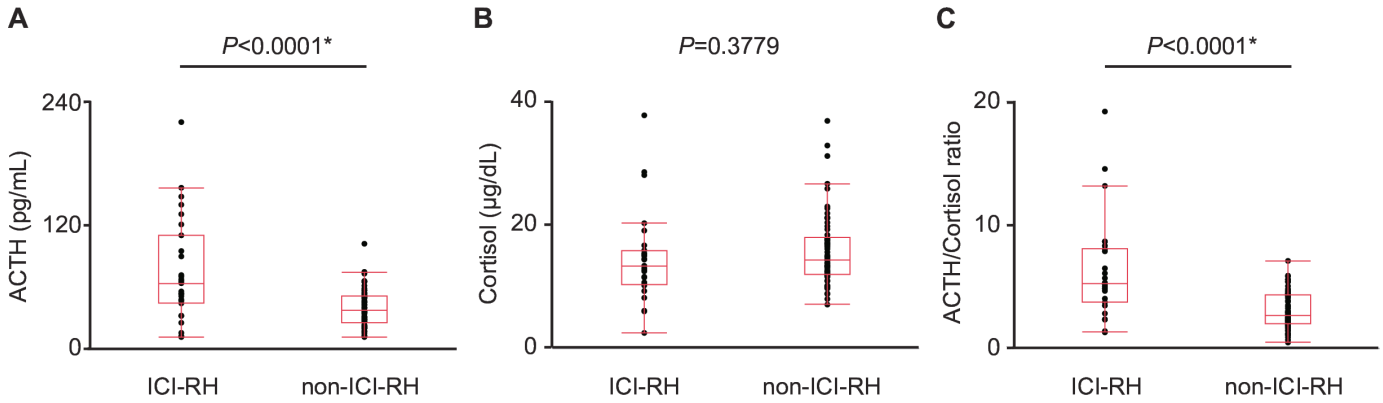

Figure 2 Differences in peak concentrations of ACTH and cortisol, and ACTH/cortisol ratio between ICI-RH (n=26) and non-ICH-RH (n=62) groups during the clinical course. (A) ACTH concentration, (B) Cortisol concentration, and (C) ACTH/cortisol ratio. ACTH, adrenocorticotropic hormone; ICI-RH, immune checkpoint inhibitor-related hypophysitis. (*: *P* <0.05)

our knowledge, this study is the first to show that a transient elevation in ACTH concentration occurs in some patients with ICI-RH. However, future studies are needed to determine the extent to which the transient elevation of ACTH levels is predictive of ICI-RH onset.

ACTH-level elevation could occur prior to ICI-RH onset. There were no differences in the clinical characteristics between the ACTH-elevated and non-elevated groups. However, these two groups may have entirely different pathogenic mechanisms. We cannot rule out the possibility that the duration of elevated ACTH levels was extremely short and could not have been measured at the time of blood collection. Na and K levels did not change at the time of peak ACTH levels. Moreover, Na and K levels at the peak were similar between the ACTH-increased and non-increased groups. The significance of ACTH-level elevation needs to be evaluated in future studies.

Three patients with elevated eosinophil fractions did not have elevated ACTH levels. In these cases, the time from ACTH peak levels to ICI-RH onset seemed to be shorter. ACTH secretion may have been impaired when ACTH and cortisol levels were measured at the peak ACTH levels in these cases. After a transient rise in ACTH, ICI-RH onset occurs at a median of 70 days, but the time to onset varies widely. When this phenomenon is observed, attention to adrenal insufficiency symptoms may prevent adrenal crisis.

This study has some limitations. First, it is a retrospective study with a small number of cases. The follow-up period after initiation of ICI tended to be slightly longer in the ICI-RH group than in the non-ICI-RH group, but the difference was not significant (p=0.082). The fact that there was no significant difference in the follow-up duration may suggest that the number of cases in this study is small, given the better prognosis in ICI-RH-onset cases in previous reports.[1] In addition, we could not collect a detailed history of steroid use at other institutions. Therefore, we cannot exclude the possibility that some of the transient elevations in ACTH levels were associated with steroid withdrawal.[16] As for the lack of increase in cortisol levels, changes in cortisol levels could have been identified by more sensitive methods such as nocturnal cortisol or urinary cortisol measurements.

If the observed lack of cortisol elevation is real, several scenarios for ACTH-level elevation without cortisol level elevation are possible. One possibility is that a bioinactive form of ACTH is abundant. ACTH is produced from proopiomelanocortin (POMC) and has several isoforms. ACTH(1-24) has steroidogenic activity, whereas ACTH(22-39) is less steroidogenic than ACTH(1-24).[17] If elevated ACTH levels have weak steroidogenic activity, ACTH(22-39) is the main elevated form. This matches the data showing that ACTH-level elevation is dominant and cortisol level elevation is weak. The second possibility is the effluence of bioinactive ACTH from tumor tissue.[18] Recent studies have indicated that paraneoplastic syndrome could be the pathophysiology of ICI-RH.[19 20] Tumor tissues express POMC/ACTH ectopically as shared epitopes, and immunological responses toward not only the tumor tissue but also the pituitary gland cause ICI-RH.[14] ICI administration may have damaged tumor cells, and tumor-derived ACTH may have been measured if it leaked into the bloodstream. Further prospective studies based on large case series are needed to clarify these mechanisms. Transient elevation of ACTH levels may provide insights into the pathogenesis of ICI-RH.

In conclusion, a transient elevation in ACTH levels occurred in some patients with ICI-RH before the onset of secondary adrenal insufficiency. Monitoring trends in ACTH levels could help predict the onset of ICI-RH.

Correction notice This article has been corrected since it was first published. The title has changed from 'Fluctuations in serum adrenocorticotropic hormone concentration may predict the onset of immune checkpoint inhibitor-related hypophysitis' to 'Fluctuations in plasma adrenocorticotropic hormone concentration may predict the onset of immune checkpoint inhibitor-related hypophysitis'.

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Contributors All authors contributed to the article and approved the submitted version. HB and GI conceived of and designed the study. HB and MY collected the data from electronic medical records. MY, YS, YO, MK, YT, YO-Y and MT interpreted the data and contributed to the discussion. HB performed the experiments and analyzed the data. HB wrote the manuscript and prepared all figures and tables. MY, SU, MS, NY and GI edited the manuscript. HF and WO provided advise for the study and contributed to the critical revision of the manuscript for important intellectual content.

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