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ORIGINAL

Reversible impairment of the processing of proopiomelanocortin into ACTH in pituitary enlargement suspected of lymphocytic hypophysitis

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Abstract. We describe a 64-year-old woman with a cystic pituitary mass presenting with central diabetes insipidus. Brain magnetic resonance imaging (MRI) with enhancement showed enlargement of the pituitary gland with cystic portions and thickening of the pituitary stalk with homogeneous enhancement. Combined anterior pituitary stimulation test and insulin-induced hypoglycemic test confirmed the diagnosis of panhypopituitarism, including adrenocortical insufficiency due to pituitary and hypothalamic dysfunction by stalk compression. Interestingly, the response of serum cortisol to CRH was low and delayed, in contrast to the marked increase in plasma ACTH. Molecular analysis of her plasma ACTH by Sephadex G75 gel exclusion chromatography coupled with radioimmunoassay (RIA) indicated a peak for high molecular weight ACTH, i.e., proACTH, in addition to that for 1-39 ACTH. Three years later, enlargement of the pituitary gland with cystic portions and thickening of the pituitary stalk disappeared completely, followed by the decrease in plasma proACTH level. By the results of endocrinological study and the change of pituitary MRI findings, lymphocytic hypophysitis was suggested. Synthesis of immature ACTH is generally thought to be due to impaired processing of the precursor proopiomelanocortin (POMC) through activation of prohormone convertase (PC)-1 by CRH. It is possible that the immature ACTH in this case was produced by impaired processing of the precursor POMC due to decreased CRH, dysfunction of corticotrophs in the anterior pituitary by compression of the normal pituitary, or antibodies targeting hypothalamic and/or pituitary cells. This report suggested that impaired processing of POMC may unusually play a role in adrenocortical insufficiency exhibited in lymphocytic hypophysitis.

Key words: Lymphocytic hypophysitis, Central diabetes insipidus, Hypothalamic adrenocortical insufficiency, proACTH, Proopiomelanocortin (POMC)

LYMPHOCYTIC hypophysitis is an uncommon autoimmune disease in which the pituitary gland is enlarged secondary to inflammatory infiltration with lymphocytes, plasma cells and macrophages, and atrophic due to destruction of pituitary tissue and replacement by fibrosis [1]. Lymphocytic adenohypophysitis, described as a typical subtype of lymphocytic hypophysitis, occurs mainly in women and is often seen in the later stages of pregnancy [2]. Many patients present with headaches or visual field impairment due to extrasellar pituitary enlargement and impaired secretion of one or more pituitary hormones showing varying degrees of pituitary dysfunction [3]. Lymphocytic hypophysitis is considered a syndrome including disorders of the anterior pituitary, which presents with hypopituitarism (lymphocytic adenohypophysitis), and of the posterior pituitary which presents with central diabetes insipidus (lymphocytic infundibuloneurohypophysitis). The detection of higt molecular weight ACTH has not been reported in lymphocytic hypophysitis. High molecular weight ACTH is thought to be produced by impaired processing of the precursor proopiomelanocortin (POMC) into ACTH in various disease states, such as ACTH-producing adenoma and ectopic ACTH syndrome. Here, we report a 64-year-old woman with pituitary enlargement suspected of lymphocytic hypophysitis, who exhibited hypothalamic adrenocortical insufficiency, with secretion of proACTH as well as authentic 1-39 ACTH.

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Case Report

In February 2006, a 64-year-old woman was admitted to our hospital, complaining of thirst, polyuria and polydipsia that had persisted for one month. She had no relevant medical history and no family history of diabetes mellitus, hypertension, pituitary disease, or diabetes insipidus. She was a nonsmoker and did not drink alcohol. She was married at the age of 24 and had two children after normal pregnancies without massive bleeding or postpartum abnormalities. She had never been on medication until this admission. On admission, she was conscious. She was 150.5 cm in height and weighted 60.0 kg. She showed a normal distribution of body hair, and the goiter was not palpable. The results of clinical examination, including body temperature and blood pressure, were normal. The 24-h urinary output was 4.0-5.0 liters with an intake of 6.0-6.5 liters. Laboratory findings are shown in Table 1. Plasma osmolality was 295 mmol/kg, but urinary osmolality was 129 mmol/kg. Cranial and pituitary magnetic resonance imaging (MRI) with gadolinium contrast showed enlargement of the pituitary gland with cystic portions, and thickening of the pituitary stalk with homogeneous enhancement. There was loss of the "bright spot" of the posterior pituitary gland on T1-weighted MRI without gadolinium contrast (Fig. 1). Ga scintigraphy showed increased uptake in the pituitary gland (Fig. 2). The patient had neither headache, visual disturbance, nor galactorrhea. Neurohypophyseal function was evaluated by water deprivation test. After 8 h of water restriction, the urinary osmolality remained between 247 and 452 mmol/kg, and the plasma arginine vasopressin (AVP) level was not increased (Table 2). After desmopressin acetate (DDAVP) loading test, the urinary osmolality rose from 320 to 625 mmol/kg (Table 2). These data and MRI findings were compatible with a diagnosis of central diabetes insipidus. The results of endocrinological examination are shown in Table 3. Basal plasma ACTH measured using an

Table 1 Laboratory data on admission

Urinalysis		Blood chemistry		BUN	10.5 mg/dL
color	yellow	CRP	0.1 mg/dL	Cr	0.6 mg/dL
pH	7.5	TP	6.8 g/dL	UA	4.6 mg/dL
protein	(-)	Alb	67.0 %	FPG	85 mg/dL
occult blood	(-)	α1	2.9 %	HbA1c	5.4 %
glucose	(-)	α2	8.7 %	plasma osmolality	295 mOsm/kgH_2O
ketone body	(-)	β	11.3 %		
osmolality	129 mOsm/kgH_2O	γ	10.1 %		
		AST	20 IU/L		
		ALT	24 IU/L	Blood gas analysis	
		LDH	251 IU/L	pH	7.384
Hematological exam		ALP	239 IU/L	pCO_2	38.7 mmHg
WBC	4300 /μL	γ-GTP	32 IU/L	pO_2	83.4 mmHg
Neu	47.9 %	CPK	140 IU/L	HCO_3	25.0 mmol/L
Lym	45.7 %	T-Cho	209 mg/dL	BE	2.5 mmol/L
Mo	4.1 %	TG	112 mg/dL	SaO_2	97.6 %
Eo	1.8 %	HDL-C	58 mg/dL		
Ba	0.5 %	Na	138 mEq/L		
RBC	426 ×10^4/μL	K	4.4 mEq/L		
Hb	13.2 g/dL	Cl	102 mEq/L		
Ht	38.6 %	Ca	9.4 mEq/L		
Plts	26.6 ×10^4/μL	P	4.9 mEq/L		

Underlined values represent outside of reference ranges. Osm, Osmolality; WBC, White blood cell count; Neu, Neutrophil count; Lym, Lymphocyte count; Mo, Monocyte count; Eo, Eosinophil count; Ba, Basophil count; RBC, Red blood cell count; Hb, Hemoglobin; Ht, Hematocrit; Plts, platelets; CRP, C-reactive protein; TP, Total protein; Alb, Albumin; α1, α1-globurin; α2, α2-globurin; β, β-globurin; γ, γ-globurin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; CPK, Creatine phosphokinase; T-Cho, Total cholesterol; TG, Triglyceride; HDL-C: High-density lipoprotein cholesterol; BUN, Blood urea nitrogen; Cr, Creatinine; UA, Uric acid; FPG, Fasting plasma glucose; HbA1c, Hemoglobin A1c; pCO_2, partial pressure of CO_2; pO_2, partial pressure of O_2; BE, Base excess; SaO_2, Saturation of arterial blood oxygen

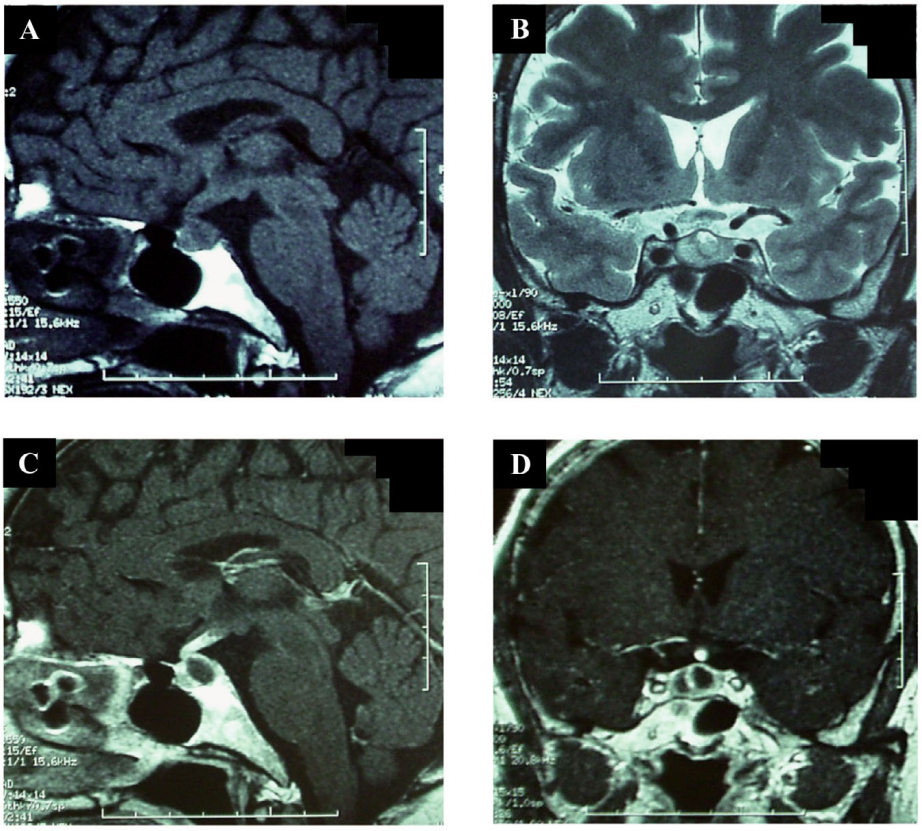

Fig. 1 MRI of the pituitary gland on admission. (A) Sagittal T1-weighted imaging without gadolinium (Gd) contrast. Loss of the "bright spot" of the posterior pituitary gland was observed. (B) Coronal T2-weighted imaging without Gd contrast. (C) Sagittal T1-weighted imaging with Gd contrast suggested cystic enlargement of the pituitary gland with peripheral rim enhancement, and thickening of the pituitary stalk with homogeneous enhancement. (D) Coronal T1-weighted imaging with Gd contrast.

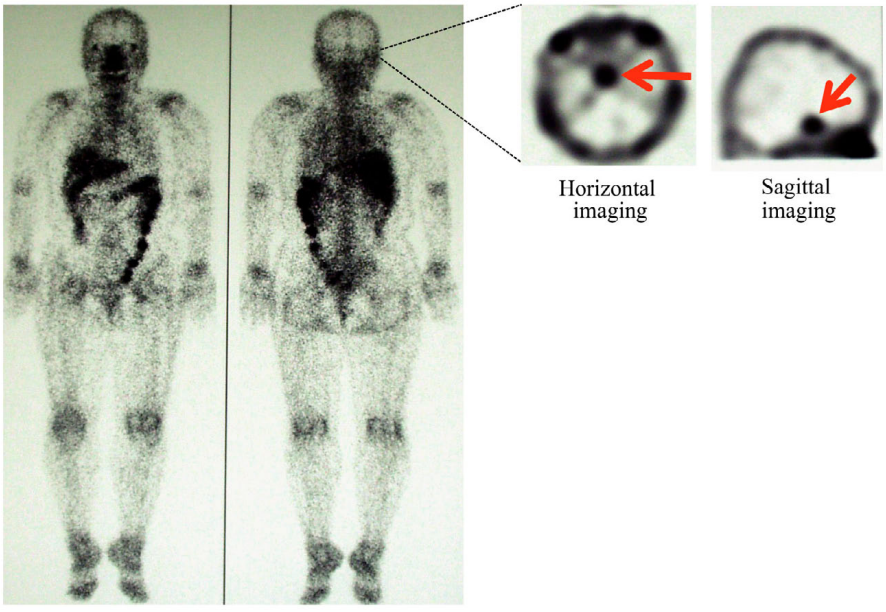

Fig. 2 Ga scintigraphy. Increased uptake was observed in the pituitary gland (arrows).

Table 2 Endocrinological provocation tests

Daily profile of plasma ACTH and cortisol levels

	8:00	12:00	16:00	20:00	0:00
ACTH (pg/mL)	8.3	8.3	11.0	16.3	8.3
cortisol (μg/dL)	0.2	0.2	0.3	0.9	0.2

Water deprivation test

Time (hours)	0	1	2	3	4	5	6	7	8
Urine Osm (mOsm/kg)	205.0	344.0	310.0	345.0	247.0	320	288	385	452
Plasma Osm (mOsm/kg)	300.0			306.0					302
ADH (pg/mL)	0.6			0.8					0.3

ADH, Antidiuretic hormone

Desmopressin acetate (DDAVP) loading test

Time (minutes)	0	30	60	90	120
Urine Osm (mOsm/kg)	329	385	536	652	656
Plasma Osm (mOsm/kg)	306				292

CRH+GRH+LHRH+TRH loading test

Time (minutes)	0	15	30	60	90	120
ACTH (pg/mL)	11.4	157	224	179	162	144
cortisol (μg/dL)	0.3	3.3	5.3	7.8	8.7	9.6
GH (ng/mL)	0.99	3.4	4.92	6.28	4.54	3.21
LH (mIU/mL)	0.1	0.3	0.5	0.8	1	0.1
FSH (mIU/mL)	1.7	3.2	4.2	6.5	8	5
PRL (ng/mL)	31.6		44.8	43.3		32.5
TSH (μIU/mL)	0.1		0.2	0.2		0.1

CRH (100 μg), GRH (100 μg), TRH (500 μg), and LH-RH (100 μg) were intravenously injected.

Insulin tolerance test

Time (minutes)	0	15	30	45	60	90	120
plasma glucose (mg/dL)	70	31	43	47	59	58	67
ACTH (pg/mL)	13.7	23.6	43.1	31	25.5	18.7	18.6
cortisol (μg/dL)	9.7	6.5	22.3	24.2	21	20	15.7
glucagon (pg/mL)	164	180	256	179	199	168	167
GH (ng/mL)	0.3	0.1	0.5	1.3	1.9	1.2	0.4

Prolonged ACTH stimulation test

Time (days)	1	2	3	4	5
u-OHCS (mg/day)	5.8	27	33	53.1	22.3
u-KS (mg/day)	2.8	5.3	7	12.6	6.1
u-cortisol (μg/day)	46.3	1916.3	2305.4	2823.5	1500.6

ACTH-Z (1.0mg) was intramuscularly injected in the mornings of day 2, day 3 and day 4.

ACTH kit (Mitsubishi Chemicals Corp., Tokyo, Japan) that excludes high molecular weight ACTH extending to the C-terminus (normal range 7.2-63.3pg/mL) was normal, while basal serum cortisol level was low without normal circadian fluctuation. Oliguria and increased urinary osmolality were occasionally observed, followed by the addition of hypoadrenocortism to diabetes insipidus, i.e., "masked diabetes insipidus." Basal plasma PRL was slightly elevated. After administration of 100 μg of CRH, plasma ACTH level increased markedly, while the response of serum cortisol was low and delayed. Plasma TSH, GH, FSH, and LH responses to appropriate stimuli were blunted (Table 2). To estimate hypothalamic function, insulin tolerance test was performed. Plasma ACTH response to insulin (0.1 unit/kg)-induced hypoglycemia was slightly blunted (Table 2). Urinary 17-OHCS, 17-KS, and free cortisol excretion showed good responses to daily administration of ACTH-Z (1.0 mg/day, intramuscularly, 3 days) (Table 2). Based on these endocrinological examinations, we made a diagnosis of adrenocortical insufficiency caused by hypothalamic and pituitary dysfunction. We next investigated the origins of pituitary gland enlargement in this case. The levels of serum angiotensin-converting enzyme (ACE), the tumor marker α-fetoprotein (AFP), and human chorionic gonadotropin (hCG)-β were not increased. Anti-nuclear antibodies (ANA), proteinase 3-antineutrophil cytoplasmic antibodies (PR3-ANCA), and myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) were negative (Table 3). Results of chest x-ray examination were normal. Therefore, pituitary nodular lesions including sarcoidosis, germinoma, and granulomatous hypophysitis, were excluded. She refused pituitary biopsy, and selected watchful waiting to observe the clinical course of the pituitary mass. Clinical examination and MRI findings suggested lymphocytic hypophysitis, including anterior hypophysitis and infundibuloneurohypophysitis. Anti-pituitary antibody was negative. As the response of serum cortisol was low in contrast to the marked increase in plasma

Table 3 Endocrinological and autoimmunological examination on admission

FT3	2.8 pg/mL	AFP	2.2 ng/mL
FT4	0.8 ng/dL	hCG	<0.4 mIU/mL
IGF-1	284.9 ng/mL	hCG-β	<0.1 ng/mL
DHEA-S	274 ng/mL	sIL-2R	125 U/mL
plasma renin activity	0.4 ng/mL/hr	PR3-ANCA	<1.3 U/mL
aldosterone	8.2 ng/dL	MPO-ANCA	<1.3 U/mL
adrenalin	<0.010 ng/mL	anti-pituitary antibody	negative
noradrenalin	0.23 ng/mL	antinuclear Antibody	<×80
dopamin	<0.010 ng/mL	anti-SS-A antibody	negative
ACE	11.7 U/L	anti-SS-B antibody	negative
IgG4	22 mg/dL	anti-Thyroid Peroxidase Antibody	<0.3 U/mL
CEA	1.5 ng/mL	anti-Thyroglobulin Antibody	<0.3 U/mL

FT3, Free triiodothyronine; FT4, Free thyroxine; IGF-1, Insulin-like growth factor-1; DHEA-S, dehydroepiandrosterone sulfate; ACE, Angiotensin-converting enzyme; CEA, Carcinoembryonic antigen; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; sIL-2R, soluble interleukin-2 receptor; PR3-ANCA, Proteinase3-antineutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies

Urine hormonal values	
u-free cortisol	55.6 μg/day
u-17-OHCS	2.20 mg/day
u-17-KS	2.00 mg/day

17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroid

ACTH after administration of CRH, it was possible that her plasma ACTH had low bioactivity. Sephadex G75 gel exclusion chromatography was performed to determine the size of her plasma ACTH (kindly performed by Dr. Yutaka Oki, the Second Department of Internal Medicine, Hamamatsu University School of Medicine) [4-6]. The blood samples showing the basal and peak values after administration of CRH were used for analysis. The fractionation procedure for measurement of ACTH with conventional RIA-systems was performed as described previously. A Sephadex G-75 column (1.0 × 50 cm) was used for fractionation. After freeze-drying a 1 mL plasma sample and adding 0.5 mL of elution buffer (0.1 M sodium phosphate buffer and 0.1% bovine serum albumin (BSA)), the solution was applied to the column and 1 mL fractions were collected and freeze-dried. In the RIA for ACTH, anti-1-24 ACTH rabbit serum was used as the primary antibody, and 125-I-1-39 ACTH was used as a tracer. This antiserum to ACTH did not crossreact with α-MSH or β-endorphin. The elution profiles on chromatography of her samples indicated that the basal value after administration of CRH showed two peaks, one of which was eluted at the same position as 1-39 ACTH and the other before the 1-39 ACTH position, indicating a high molecular weight form (Fig. 3). The latter did not show crossreactivity with β-endorphin. Therefore, these results indicated the presence of proACTH other than 1-39 ACTH in her plasma. When calculated with the area under the curve, the molecular ratio of proACTH was 38.0% of all measurable ACTH.

She was prescribed intranasal desmopressin at a dose of 10 μg/day, and the polyuria and polydipsia were well controlled. Replacement therapy with hydrocortisone or L-thyroxine was not initiated, because she was well and had no symptoms suggestive of glucocorticoid deficiency and hypothyroidism. On MRI 3 years later, enlargement of the pituitary gland with cystic portions and thickening of the pituitary stalk disappeared completely (Fig. 4). Basal concentrations of the pituitary anterior hormones, such as ACTH, TSH, PRL, FSH, and LH, were normal. The responses of anterior pituitary stimulation tests improved (Table 4). Moreover, no marked increase was observed in plasma ACTH after administration of CRH, and the molecular ratio of proACTH was decreased to 11.5% of all measurable ACTH (Fig. 3). The improvement of pituitary function was gradually induced following regression of the pituitary lesions on MRI (Table 5). However, posterior pituitary dysfunction failed to improve.

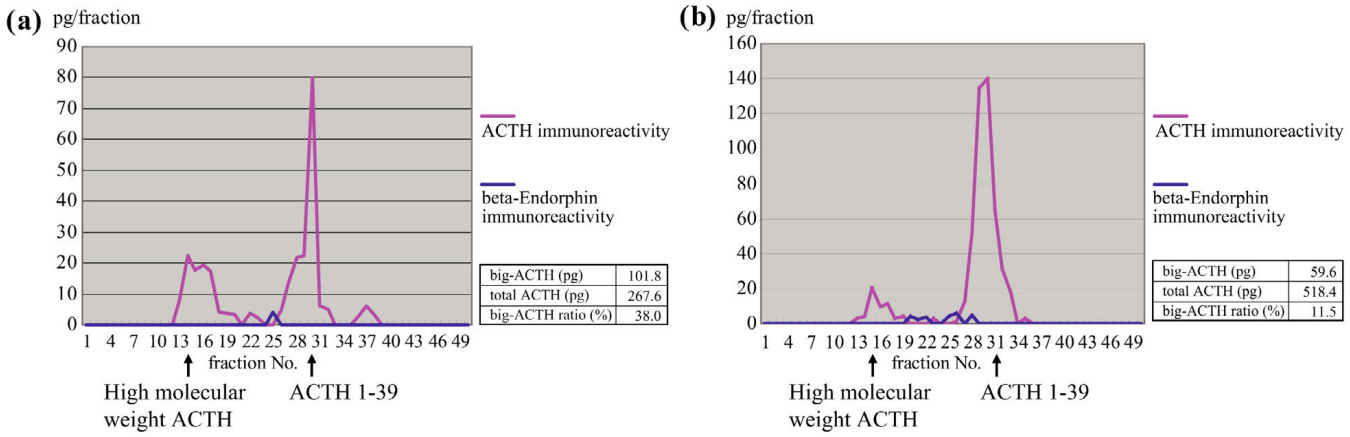

Fig. 3 ACTH immunoreactivity (pg/fraction) of patient plasma on Sephadex G-75 gel filtration. (a) On admission, two peaks were observed, one of which was eluted at the same position as 1-39 ACTH, while the other was eluted before the 1-39 ACTH position, indicating a high molecular weight form of ACTH. (b) Three years after onset, the molecular ratio of high molecular weight form of ACTH was decreased with the disappearance of pituitary lesions on MRI.

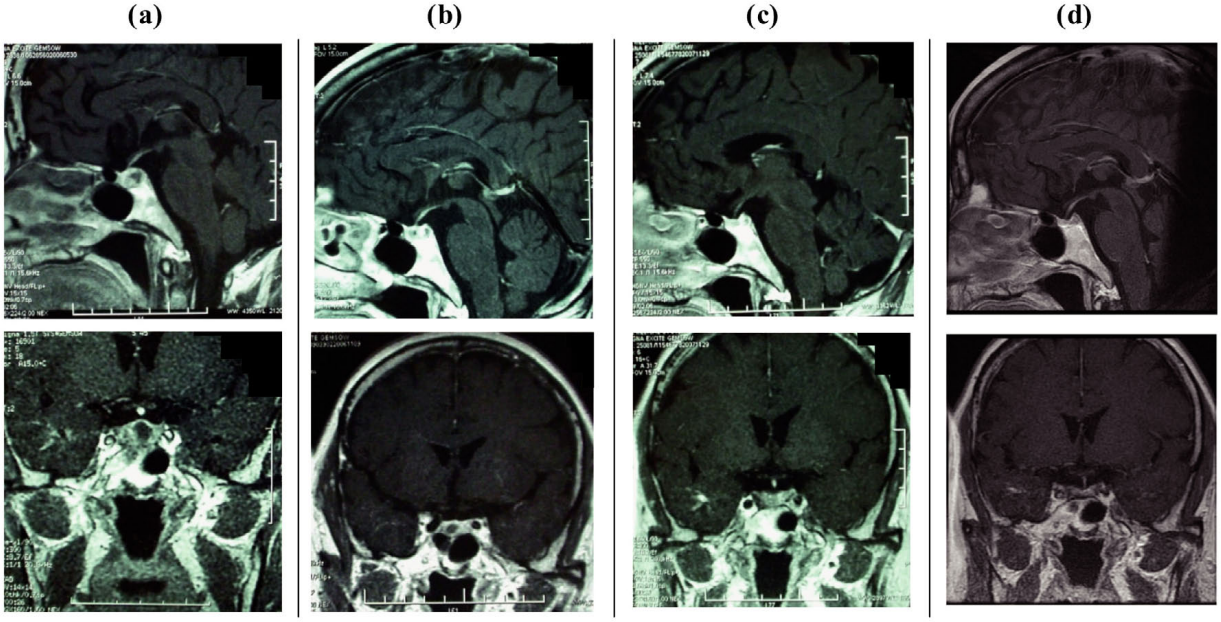

Fig. 4 Time course of changes in MRI findings after manifestation of disease. Top: Sagittal T1-weighted image with gadolinium contrast; Bottom: Coronal T1-weighted image with gadolinium contrast. (a) Four months after onset of central diabetes insipidus. (b) Twelve months after onset. (c) Two years after onset. (d) Three years after onset.

Table 4 CRH+GRH+LHRH+TRH loading test after 36 months, on disappearance of enlargement of the pituitary gland and thickening of the pituitary stalk

Time (minutes)	0	15	30	60	90	120
ACTH (pg/mL)	39.9	95.1	84.2	60.5	43.7	57.8
cortisol (μg/dL)	7.9	15.9	15.8	13.3	9	12.7
GH (ng/mL)	0.42	7.18	7.32	3.87	1.83	0.73
LH (mIU/mL)	4.91	8.31	11.42	12.05	11.67	12.21
FSH (mIU/mL)	12.91	15.13	15.71	17.14	17.98	20.19
PRL (ng/mL)	5.93		91.66	57.82		24.73
TSH (μIU/mL)	4.57		46.5	32.3		15.4

CRH (100 μg), GRH (100 μg), TRH (500 μg), and LH-RH (100 μg) were intravenously injected.

Table 5 Time course on changes of basal pituitary hormones, cortisol, FT4 and IGF-1, and responses of pituitary hormones to appropriate stimuli with changes of MRI findings after manifestation of disease

	onset of disease	4 months after onset	12 months after onset	2 years after onset	3 years after onset
pituitary MRI findings					
enlargement of the pituitary gland	(+++)	(+++)	(++)	(+)	(-)
cystic portions in the pituitary gland	(+)	(+)	(+)	(-)	(-)
thickening of the pituitary stalk	(+++)	(+)	(-)	(-)	(-)
ACTH (pg/mL)	13.3	16.3	61.9	56.9	62.9
cortisol (μg/dL)	0.7	0.9	8.2	15.5	13.6
TSH (μIU/mL)	0.01		1.9	2.56	1.71
FT4 (ng/dL)	0.8		1.0	0.9	0.9
IGF-1 (ng/mL)	284.9		165.9	267.0	199.7
CRH+GRH+LHRH+TRH loading test					
Peak value					
ACTH (pg/mL)	224		421		95.1
cortisol (μg/dL)	9.6		23.6		15.9
GH (ng/mL)	6.28		7.71		7.32
LH (mIU/mL)	1.0		14.1		12.21
FSH (mIU/mL)	8.0		22.9		20.19
PRL (ng/mL)	44.8		19.0		91.66
TSH (μIU/mL)	0.2		35.0		46.5
Insulin tolerance test					
Peak value					
ACTH (pg/mL)	43.1		60.0		62.2
cortisol (μg/dL)	24.2		9.8		21.4
proACTH (%)	38.0				11.5

Discussion

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland, which is enlarged secondary to inflammatory infiltration with lymphocytes, plasma cells, and macrophages [1]. Lymphocytic adenohypophysitis, described as a typical subtype of lymphocytic hypophysitis, occurs mainly in women and often presents in the later stages of pregnancy, although a few cases have also been reported in postmenopausal women and in men [2, 7-10]. Although the etiology of lymphocytic hypophysitis remains to be clarified, it is considered to be due to an autoimmune mechanism [11, 12]. However, our case had no features of autoimmune diseases. Lymphocytic hypophysitis is classified according to the site of inflammation: lymphocytic adenohypophysitis (LAH), inflammation of the adenohypophysis; lymphocytic infundibuloneurohypophysitis (LINH), inflammation of the infundibulum and neurohypophysis. However, there have been some recent reports of patients presenting with both anterior and posterior pituitary dysfunction [2, 13]. Therefore, lymphocytic hypophysitis is classified as follows: LAH, LINH, and panhypophysitis [14]. It may be appropriate to consider lymphocytic hypophysitis as a syndrome involving both the anterior and posterior pituitary [13]. The most unique and prominent MRI features are the pituitary stalk thickening and marked enlargement of the pituitary gland with homogeneous contrast enhancement. In some cases, lymphocytic hypophysitis has been reported to show a cystic appearance [15, 16]. Thus, there are many variations of MRI features of lymphocytic hypophysitis. Our case showed homogeneous peripheral rim enhancement with cystic appearance, and a thickened pituitary stalk on MRI, with the absence of the high signal intensity in the normal neurohypophysis on T1-weighted images. Differential diagnoses to differentiate cystic lymphocytic hypophysitis from other pituitary diseases include pituitary adenoma, Rathke's cleft cyst and craniopharyngioma. Although pituitary biopsy and histological findings are required for definite diagnosis, the patient wished to avoid invasive tests, such as pituitary biopsy, and agreed to undergo pituitary biopsy if the pituitary mass

showed further expansion or visual disturbance by the mass was noted. In fact, pituitary biopsy was not performed in the present case, and she experienced regression of the pituitary mass three years after the onset of central diabetes insipidus. Therefore, a diagnosis of lymphocytic hypophysitis was suggested based on the clinical course.

Many patients show impaired secretion of one or more pituitary hormones presenting with varying degrees of pituitary dysfunction, such as central diabetes insipidus or panhypopituitarism, including adrenocortical insufficiency [3]. The hypothalamus contains a number of nuclei of neurons important in the regulation of hormone secretion from the pituitary. The paraventricular (PVN) and supraoptic (SON) nuclei contein neurons that produce and secrete vasopressin and oxytocin, transported to the posterior pituitary gland *via* their axons. On the other hand, the neurons of the diffuse collection of hypothalamic neurons, called the parvocellular secretary system, send their axons to the median eminence in the pituitary stalk, where their terminals release the releasing hormones such as CRH, TRH, and GnRH, and control anterior pituitary function. ACTH is synthesized in the anterior pituitary corticotrophs. CRH increases expression of the precursor POMC gene, and stimulates ACTH synthesis through activation of POMC processing by prohormone convertase (PC)-1 [17-19]. The impairment in processing of POMC leads to synthesis of immature ACTH, so-called "big ACTH."

Lymphocytic hypophysitis can show the thickened pituitary stalk, resulting in compression of vessels and neurons in the stalk. In our patient, mild elevation of prolactin level was observed. This hyperprolactinemia was probably due to the decreased dopamine delivery from the hypothalamus to the anterior pituitary gland caused by stalk compression [2]. It is possible that hypothalamic adrenocortical insufficiency in our patient was caused by stalk compression, resulting in decreased CRH delivery from the hypothalamus to the anterior pituitary gland. In addition, pituitary dysfunction might be caused by autoimmune process. It has been recently reported that the antibodies against pituitary ACTH-secreting cells and hypothalamic CRH-secreting cells were detected in idiopathic hypopituitarism patients with ACTH deficiency, and that POMC was targeted by autoantibodies in a patient with biopsy-proven IgG4-related hypophysitis [20, 21]. Her immature ACTH, i.e., proACTH, was thought to be produced by impaired processing of the precursor POMC due to the decrease of CRH, dysfunction of corticotrophs caused by compression of the normal pituitary due to inflammatory swelling and the cystic portion, or antibodies targeting hypothalamic and/or pituitary cells [19]. Lymphocytic hypophysitis often results in isolated ACTH deficiency, combined ACTH/TSH deficiencies, or multiple pituitary hormone deficiency (generally in descending order of frequency ACTH > TSH > FSH/LH > GH > PRL), although this phenomenon is still incompletely understood. Adrenocortical insufficiency caused by lymphocytic hypophysitis may be explained partly by the impaired processing of POMC, except for ACTH deficiency.

In conclusion, we reported a rare case suggestive of lymphocytic hypophysitis exhibiting hypothalamic adrenocortical insufficiency, with secretion of pro-ACTH. The unique and unusual findings in this case may open new scenarios for pituitary dysfunction in lymphocytic hypophysitis.

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Appendix

The author has no conflicts of interest.

References

1. Cosman F, Post KD, Holub DA, Wardlaw SL (1989) Lymphocytic hypophysitis. Report of 3 new cases and review of the literature. *Medicine* 68: 240-256.
2. Thodou E, Asa SL, Kontogeorgos G, Kovacs K, Horvath E, *et al*. (1995) Clinical case seminar: lymphocytic hypophysitis : clinicopathological findings. *J Clin Endocrinol Metab* 80 : 2302-2311.
3. Asa SL, Bilbao JM, Kovacs K, Josse RG, Kreines K

(1981) Lymphocytic hypophysitis of pregnancy resulting in hypopituitarism: a distinct clinicopathologic entity. *Ann Intern Med* 95 : 166-171.
4. Ratter SJ, Lowry PJ, Besser GM, Rees LH (1980) Chromatographic characterization of adrenocorticotrophin in human plasma. *J Endocrinol* 85: 359-369.
5. Yamakita N, Murai T, Kawamura S, Teramachi H, Matsuhisa T, *et al*. (1999) High molecular weight corticotropin in measured with immunoradiometric assay in a patient with asymptomatic pituitary corticotropinoma. *Endocr J* 46: 563-571.
6. Yamakita N, Murai T, Oki Y, Matsuhisa T, Hirata T, *et al*. (2001) Kuwayama A, Yasuda K. Adrenal insufficiency after incomplete resection of pituitary macrocorticotropionoma of Cushing's disease: Role of high molecular weight ACTH. *Endocr J* 48: 43-51.
7. Patel MC, Guneratne N, Haq N, West TE, Weetman AP, *et al*. (1995) Peripartum hypopituitarism and lymphocytic hypophysitis. *QJM* 88: 571-580.
8. Noto H, Tsukamoto K, Hayashi S, Takano K, Fujita T, *et al*. (2001) Spontaneous recovery from hypopituitarism in a man with lymphocytic hypophysitis: a case report. *Endocr J* 48: 483-486, 2001.
9. Tubridy N, Saunders D, Thom M, Asa SL, Powell M, *et al*. (2001) Infundibulohypophysitis in a man presenting with diabetes insipidus and cavernous sinus involvement. *J Neurol Neurosurg Psychiatry* 71: 798-801.
10. Ito K, Mukawa J, Miyagi K, Takara E, Mekaru S, *et al*. (1992) lymphocytic adenohypophysitis with sudden onset of diabetes insipidus in menopausal female: case report. *Neurol Med Chir* 32: 346-350.
11. Pestell RG, Best JD, Alford FP (1990) Lymphocytic hypophysitis. The clinical spectrum of the disorder and evidence for an autoimmune pathogenesis. *Clin Endocrinol* 33: 457-466.
12. O'Dwyer DT, Clifton V, Hall A, Smith R, Robinson PJ, *et al*. (2002) Pituitary autoantibodies in lymphocytic hypophysitis target both gamma- and alpha-enolase -A link with pregnancy? *Arch Physiol Biochem* 110: 94-98.
13. Nakamura Y, Okada H, Wada Y, Kajiyama K, Koshiyama H (2001) Lymphocytic hypophysitis : its expanding features. *J Endocrinol Invest* 24: 262-267.
14. Shimatsu A, Oki Y, Fujisawa I, Sano T (2009) Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin IgG4-related systemic disease: an emerging clinical entity. *Endocr J* 56: 1033.
15. Tamiya A, Saeki N, Kubota M, Oheda T, Yamaura A (1999) Unusual MRI findings in lymphocytic hypophisitis with central diabetes insipidus. *Neuroradiology* 41: 899-900.
16. Farah JO, Rossi M, Foy PM, MacFarlane IA (1999) Cystic lymphocytic hypophysitis, visual field defects and hypopituitarism. *Int J Clin Pract* 53: 643-644.
17. Thomas L, Leduc R, Thorne BA, Smeekens SP, Steiner DF, *et al*. (1991) Kex2-like endoproteases PC2 and PC3 accurately cleave a model prohormone in mammalian cells: evidence for a common core of neuroendocrine processing enzymes. *Proc Natl Acad Sci USA* 88: 5297-5301.
18. Seidah NG, Chretien M (1981) Complete amino acid sequence of a human pituitary glycopeptide : an important maturation product of pro-opiomelanocortin. *Proc Natl Acad Sci USA* 78: 4236-4240.
19. Kageyama K, Suda T (2008) Role and action in the pituitary corticotroph of corticotropin-releasing factor (CRF) in the hypothalamus. *Peptides* 30(4): 810-816.
20. Bellis AD, Pane E, Bellastella G, Sinisi AA, Colella C, *et al*. (2011) Detection of antipituitary and antihypothalamus antibodies to investigate the role of pituitary or hypothalamic autoimmunity in patients with selective idiopathic hypopituitarism. *Clin Endocrinol* 75: 361-366.
21. Landek-Salgado MA, Leporati P, Lupi I, Geis A, Caturegli P (2012) Growth hormone and proopiomelanocortin are targeted by autoantibodies in a patient with biopsy-proven IgG-related hypophysitis. *Pituitary* 15:412-419.