奈医誌. (J. Nara Med. Ass.) 49, 64～73, 1998

A CASE OF CUSHING'S SYNDROME ASSOCIATED WITH ISOLATED ADRENOCORTICOTROPIN (ACTH) DEFICIENCY AFTER THE REMOVAL OF CORTISOL-PRODUCING ADRENAL ADENOMA

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Received December 19, 1997

Abstract: A 45-yr-old woman with Cushing's syndrome who could not be withdrawn from postoperative hydrocortisone supplement for over 3 years after the removal of an adrenocortical adenoma is presented. This was diagnosed as associating with isolated ACTH deficiency. She had suffered from persistent severe general fatigure since 5 years prior. However, after 2 years, obesity, hypertension and moon face developed, while the malaise improved. She was then diagnosed as having Cushing's syndrome and underwent the extirpation of right adrenal adenoma. The dosage of supplementary hydrocortisone was gradually reduced after surgery. However the hydrocortisone dose could not be reduced lower than 10 mg/day after several trials of dose reduction as severe general fatigue would ensue. The pituitary function tests at postoperative 2 years and a half-year, revealed an association of isolated ACTH deficiency. It was unknown whether the isolated ACTH deficiency arose before or after the surgery.

In the present report, we discuss the association of isolated ACTH deficiency and Cushing's syndrome.

Index Terms

Isolated adrenocorticotropin deficiency, Isolated ACTH deficiency, Cushing's syndrome pituitary autoantibody

Since the first description by Sternberg[1] in 1954, cases of isolated ACTH deficiency have been increasingly reported because of the progress of specificity and sensitivity of ACTH analysis[2]. Although the etiology of the disease was not clarified, in some cases autoimmune mechanism was suspected because of having the pituitary auto-antibody[3),4),5] or lymphocyte infiltration in the pituitary gland[6),7]. As it was frequently associated with Hashimoto's disease[8),9], insulin dependent diabetes mellitus (IDDM)[10),11] or other autoimmune diseases, isolated ACTH deficiency was recognized as a disease of polyglandular autoimmune syndrome[10]. Furthermore Nussey et al.[12] speculated a cleavage enzyme defect of ACTH production in a congenital case. We experienced a case of isolated ACTH deficiency after the extirpation of adrenal adenoma of Cushing's syndrome, in which hydrocortisone could not be withdrawn over 3 years after surgery. It was difficult to differentiate it from the suppressed state of ACTH secretion by the hypercortisolism of Cushing's syndrome.

METHODS

The concentration of plasma ACTH was measured by immuno-radio-metric-assay (IRMA) kit (Allegro HS-ACTH Kit, Nihon Medical Physics Co. Ltd, Tokyo, Japan), and cortisol was measured by radio-immuno-assay (RIA) kit (Gamma Coat™ Cortisol, INCSTAR Co., USA). The normal ranges of ACTH and cortisol were 4.4~48.0 pg/ml and 4.3~10.7 μg/ml, respectively. Urinary 17-hydroxycortcosteroids (17-OHCS) and 17-ketosteroids (17-KS) were measured by colorimetry assay kit (OHAKIT and OSKIT, Kanto Chemical Co. Inc., Tokyo, Japan). The normal range of 17-OHCS and 17-KS were 2.4~5.8 mg/day and 3.3~13.8 mg/day. The intra- and inter-assay coefficients of variation of the IRMAs and RIAs were all within 10 %.

CASE REPORT

The patient (S. K.) is a 45-year-old housewife who was admitted to our department for the evaluation of facial edema and amenorrhea. At the age of her 40 years, severe malaise and amenorrhea developed and continued. Two years later, her general malaise gradually disappeared, but was replaced by weight increase and hypertension. About 1 year prior to this hospitalization, swelling of the face and leg edema initiated, which brought her to our department for examination. Her height was 161 cm, body weight was 55 kg and blood pressure was 174/90 mmHg. She demonstrated a moon face and central obesity compatible with Cushing's syndrome.

I) Urinalysis, peripheral blood examination, and biochemical examination

Urinalysis showed positive (2+) occult blood. The WBC count of peripheral blood was elevated slightly to 9,400/μl. Blood biochemical examination revealed slight elevation of GPT (52 IU/l) and elevation of LDH (740 IU/l). The serum K level was normal. The fasting blood sugar was 120 mg/dl.

Table 1. Basal Hormone Values

ACTH	<4.0 p/ml	Cortisol	27.7 μg/dl
GH	0.3 ng/ml	Sm C	138 ng/ml
LH	<0.5 mIU/ml	E_2	<10 pg/ml
FSH	6.7 mIU/ml	DHEA-S	636 ng/ml
TSH	0.7 μU/ml	T_3	78.6 ng/ml
		T_4	4.3 μg/dl
		FT_4	0.5 ng/dl
		FT_3	2.3 pg/ml
PRL	15.8 ng/ml		
PRA	<0.15 ng/ml/h	Aldosterone	37.2 pg/ml
U-17OHCS	12.8 mg/day	(2.4~5.8 mg/day)	
U-17KS	10.2 mg/day	(3.3~13.8 mg/day)	
U-KGS	5.7 mg/day	(3.5~11.2 mg/day)	

Dexamethasone Suppression test

	Cortisol	ACTH
Bf.	21.1 μg/dl	<4.0 pg/ml
2mg	31.5 μg/dl	<4.0 pg/ml
8mg	24.6 μg/dl	<4.0 pg/ml

II) **Basal hormone values and dexamethasone suppression test (Table 1)**

ACTH was <4.0 pg/ml, below detectable limits. Cortisol level was 27.7 μg/dl. The growth hormone (GH) level was normal. Somatomedine C, 138 ng/ml, was low compared with the levels of her age group. Although LH, FSH and E_2 were low, and the LH and FSH response to LH-RH provocation test showed response. The T_4, Free T_4 and Free T_3 showed below the normal levels. The TSH to TRH provocation test showed low response, 0.3 to 3.4 μU/ml. Plasma renin activity (PRA) was low. The level of 17-OHCS was high and those of 17-KS and 17-KGS were within normal range. The dexamethasone test revealed no suppression of plasma cortisol by the dose of both 2 mg and 8 mg of dexamethasone.

III) **Image diagnosis**

1) Ultrasonic examination of the abdomen (Fig. 1): An oval hypoechoic tumor (26.3×15.5 mm) was found in the region of the right adrenal gland. Adjacent to it, another tumor (24.5×18.0 mm) was observed beneath the liver as if enclosed in it. It was difficult to recognize its relation to the adrenal tumor.

2) CT of the abdomen (Fig. 2-a, 2-b): A tumor of 2.5×1.8 mm in size on the right adrenal gland and another tumor 2.5×2.0 mm in size enclosed in the liver were found.

3) Adrenal scintigram: A pronounced uptake of radio-isotope on the right and low uptake on the left were observed.

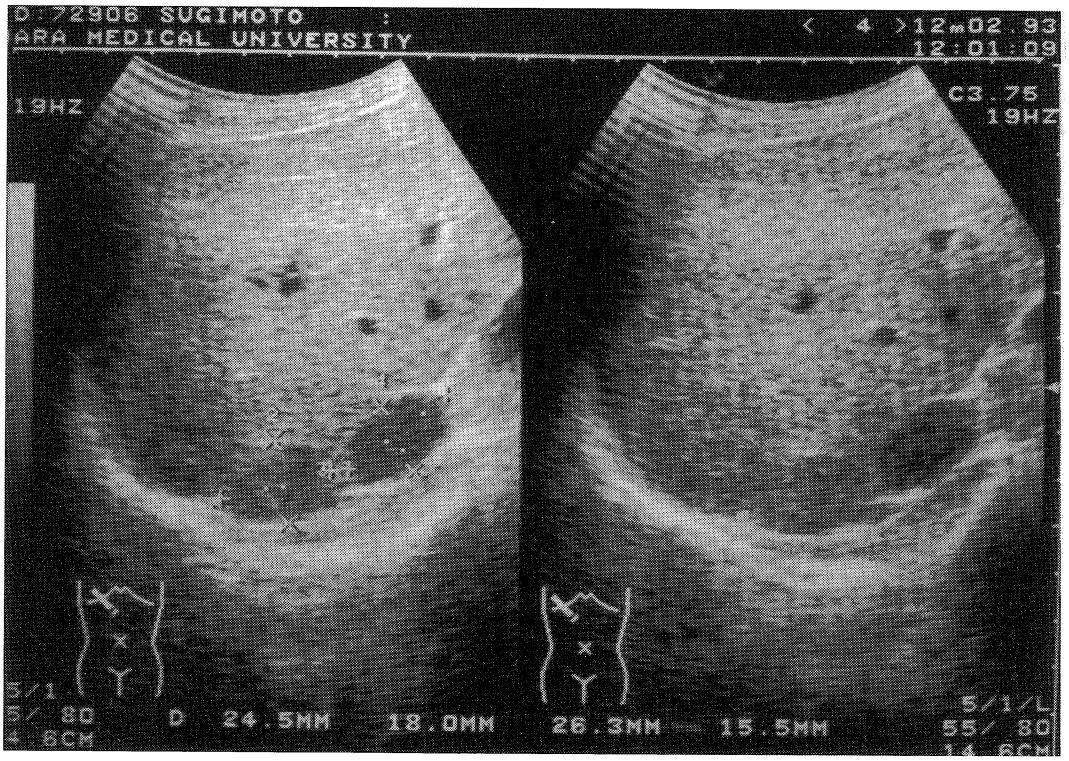

Fig. 1. Ultrasonic examination of abdomen shows an oval hypoechoic tumor (26.3× 15.5 mm) in the upper-portion of the rigth adrenal gland and another tumor (24.5×18.0 mm) was found beneath the liver like enclosed in it.

4) Adrenal angiography : Shifting of the right adrenal artery was observed and in the venous phase, polymorphic tumor staining was found.

On the basis of theses findings, a diagnosis of Cushing's syndrome due to right adrenal tumor was made. In the ultra-sonogram and the CT findings, it was difficult to determine whether the adrenal tumor and the adjacent tumor were single tumor or double tumors. It was speculated that the tumors were either solitary yet polymorphic adrenal tumor, or two homochronus tumors, or complication of the other abdominal tumors.

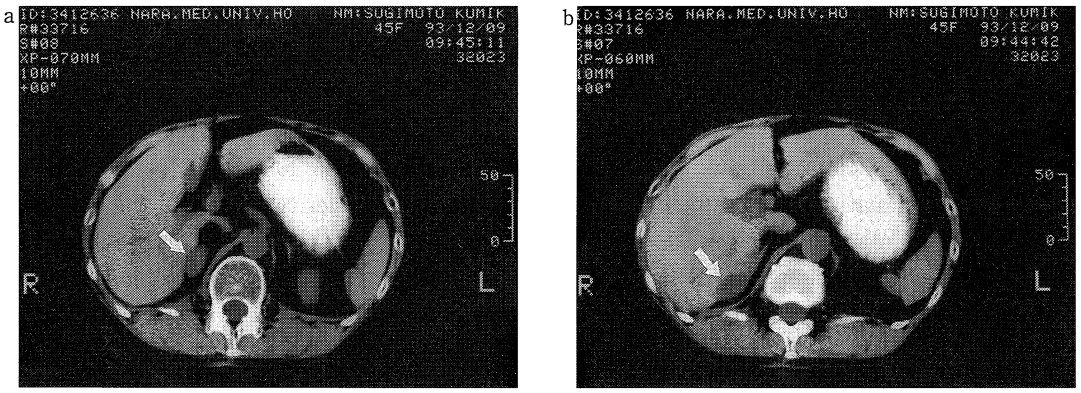

Fig. 2. CT of the abdomen. a : An oval low density tumor (2.5×1.8 mm) is found in the region of right adrenal gland. b : Another low density tumor (2.5×2.0) is detected enclosing in the liver.

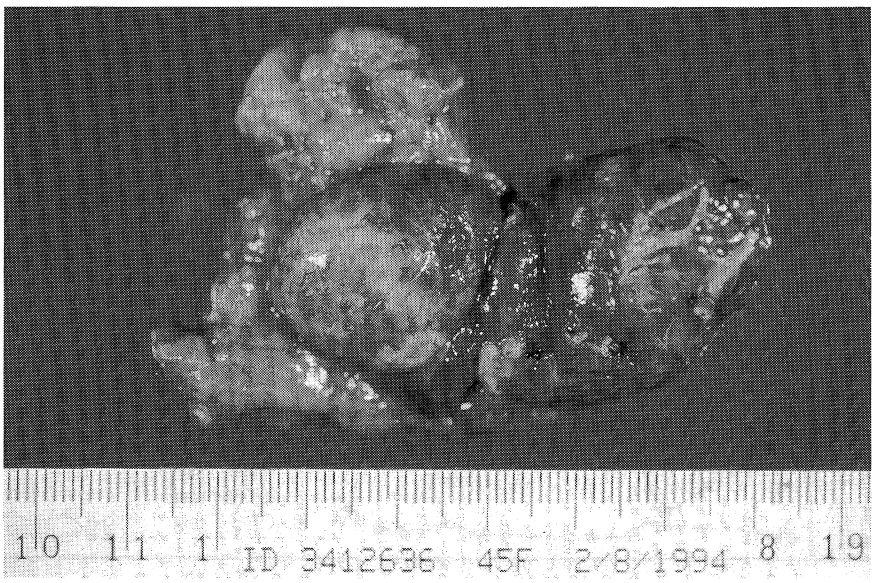

Fig. 3. Macroscopic findings of excised tumor. The tumor is encapsulated and is single isolated mass but constricted in its center like having 2 heads.

IV) **Macroscopic findings of excised tumor : Fig. 3**

It was a single isolated encapsulated tumor with 2 heads and constricted at its center. The cut surface showed dark brown. The adrenal gland excised with the tumor showed slight atrophy of the cortex. However, multiple nodular lesion like nodular hyperplasia was not found. Histologically, the tumor was compatible with cortisol-producing adrenocortical adenoma in which the compact cell and clear cell were intermingled with each other.

V) **Postoperative course (Fig. 4)**

Large amounts of hydrocortisone were administered post- operatively as usual initial replacement. From one week after the surgery hydrocortisone supplement was reduced to 30 mg/day and continued at the dosage for one month. Then the dose was reduced to 20 mg/day, by stages. As the patient complained of severe general malaise and finger stiffness, hydrocortisone was tentatively increased to 30 mg/day until at the postoperative 5th month, and then again reduced in stages. At the postoperative 6th month, her menses resumed and have continued normally. From the postoperative 1st year, the supplementary dose was reduced to 15 mg/day. The marked general malaise persisted. The plasma cortisol and ACTH levels were low before hydrocortisone administration, which was reduced to 10 mg/day before the one week of the evaluation. The same evaluation were performed over two years of the operation month after month, and no elevation were found in both plasma ACTH and cortisol levels. In suspicion of complication with hypopituitarism, the pituitary function test were performed.

VI) **Post-operative examination of pituitary-adrenal function (two and a half years after**

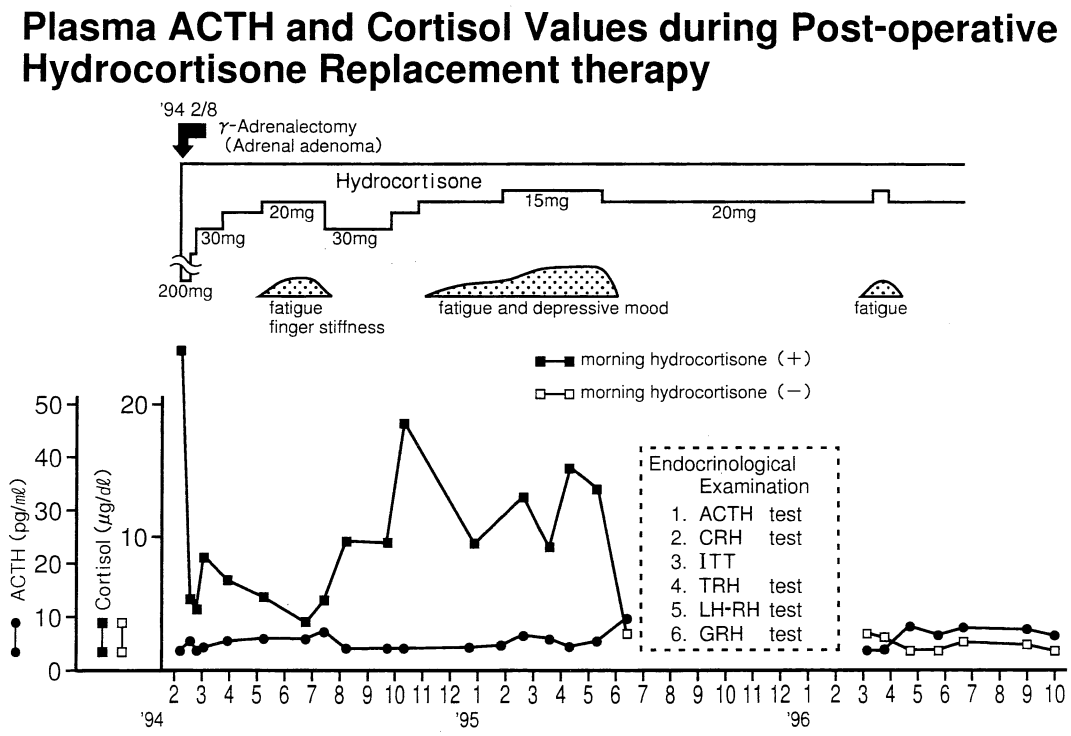

Fig. 4. Postoperative clinical course and plasma ACTH

operation)

1) ACTH test : ACTH-Z 40 U (1.0 mg) was injected for 3 consecutive days. The levels of urinary 17-OHCS and 17-KS were elevated to 8.6 mg/day and 3.5 mg/day, respectively.
2) CRH test (Fig. 5): 100 μg of CRH was infused intravenously. Plasma ACTH, cortisol and β-Endorphin levels showed no elevation.

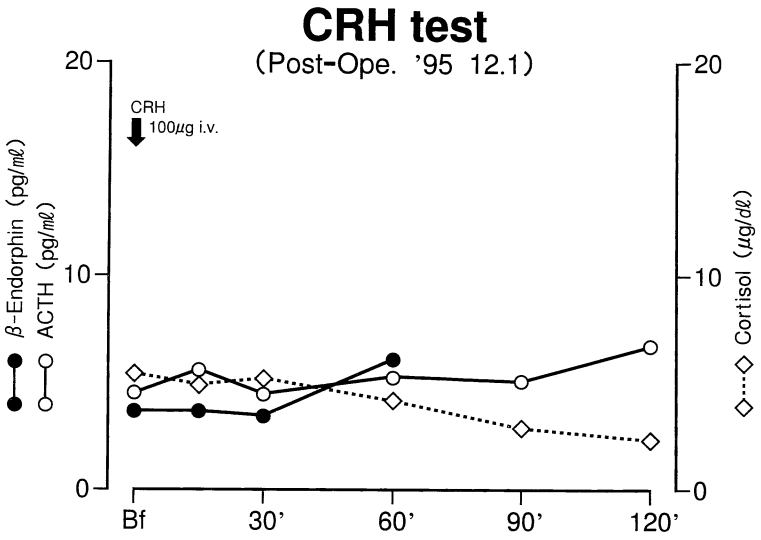

Fig. 5. Plasma ACTH, cortisol and β-Endorphin response to intravenous infusion of CRH (100 μg).

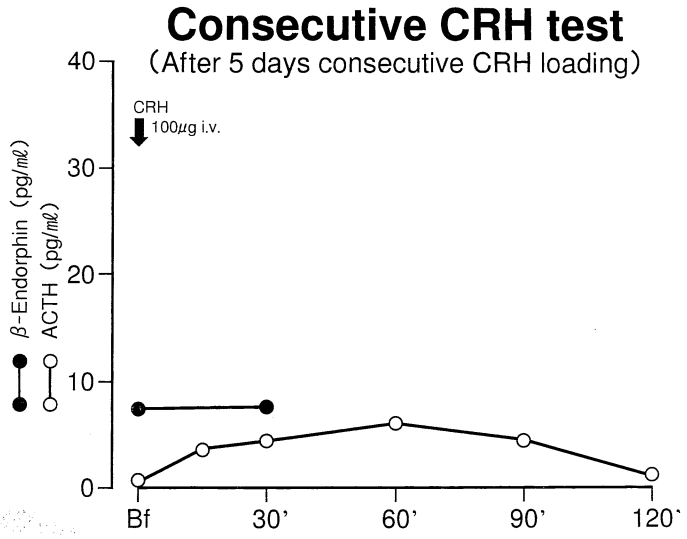

Fig. 6. Plasma ACTH and β-Endorphin response after 5days consecutive CRH loading.

3) Consecutive CRH test (Fig. 6): 100 μg of CRH was drip infused during 30 minutes for 5 consecutive days. On the 5th day, the CRH test was performed. The ACTH demonstrated low response and the peak ACTH level was as low as 5.8 pg/ml.
4) ITT (insulin tolerance test): The levels of ACTH, cortisol and GH were determined before and after injection of 5 units of regular insulin. ACTH showed low response (4.6 to 7.7 pg/ml). Cortisol showed no elevation. GH also demonstrated low response (0.8 to 4.4 ng/ml).
5) GRH test (examined 3 years after operation): 100 μg of GRH was infused intravenously. The GH showed normal response (0.5 mg/ml to 44.6 ng/ml).
6) LH-RH test and TRH test : The peak values of LH and FSH to LH-RH provocation test were 20.7 mIU/ml and 12.6 mIU/ml, respectively. TRH test performed normal TSH response (9.4 to 22.4 μU/ml).

As described above, the levels of ACTH were not elevated for more than 2 years after surgery. Consequently, the case was diagnosed as isolated ACTH deficiency associated with Cushing's syndrome after surgery.

Under the diagnosis of isolated ACTH deficiency, hydrocortisone had been supplemented at

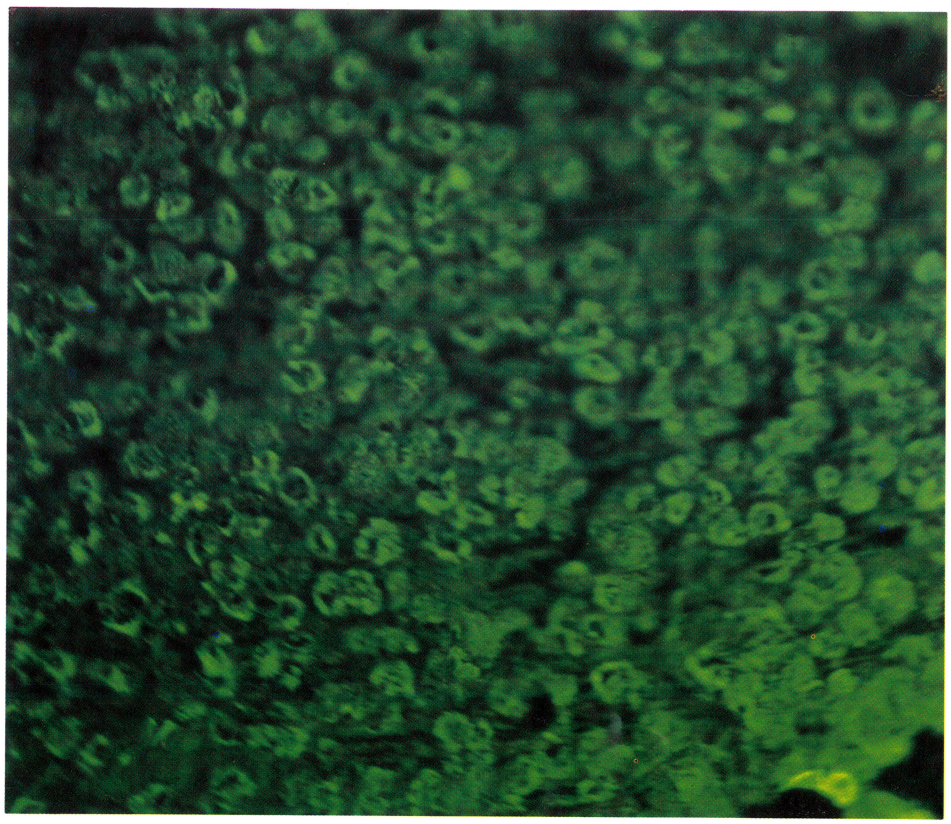

Fig. 7. Indirect fluorescent antibody method using pig pituitary gland. Fluorescein isothiocyanate (FITC) bound anti-human IgG (rabbit) is depositing on the pituitary cell surface.

a dose of 20 mg/day thereafter. Subsequently, dose reduction of the hydrocortisone was tried, but with the reduction, malaise and depression emerged, characteristic of steroid withdrawal syndrome. Moreover, the levels of ACTH and cortisol before low dose of hydrocortisone administration have been followed-up since then. The levels of ACTH and cortisol under the low supplement dose of hydrocortisone were examined over 3 years after the operation, and no elevation was found.

Ⅶ) **Study for the cause of isolated ACTH deficiency**

Before surgery, MRI revealed no abnormality of the pituitary gland, pituitary stalk and hypothalamic region. Moreover, the MRI at post-operative 2nd year did not reveal any abnormal findings. For the evaluation of the pituitary antibody, indirect fluorescent antibody method by using pig pituitary gland was performed. Fluorescein bound anti-human IgG was deposited on the surface of pig pituitary cells (Fig. 7). These findings indicated that the patient had pituitary autoantibody.

DISCUSSION

The most important problem is whether this ACTH hyposecretion can be diagnosed as isolated ACTH deficiency or not. This hyposecretion of ACTH has another probability due to the hypercortisolism induced by Cushing's syndrome or hydrocortisone supplementation.

In almost all cases of Cushing's syndrome, hydrocortisone supplement can be withdrawn around the postoperative 1st year. However, in this case, the hydrocortisone dose could not be reduced to less than 10 mg/day because of steroid withdrawal syndrome, even 3 years after surgery. In such a case, it is difficult to conclude that inhibition of ACTH secretion could persist before surgery by hypercortisolism of Cushing's syndrome, or due to even low doses of hydrocortisone, or due to isolated ACTH deficiency. During the therapeutic course, hydrocortisone reduction, as low as 10 mg/day, had been attempted many times but failed. So the examination was performed to clarify whether the case is accompanying isolated ACTH deficiency or not. In view of the result of CRH test and positive pituitary autoantibody, this case could be diagnosed as isolated ACTH deficiency.

Another interesting point in this case is when the isolated ACTH deficiency initiated. Concluding this question, the following are considered as likelifoods:

1. This isolated ACTH deficiency might have been present prior to the onset of Cushing's syndrome.
2. This isolated ACTH deficiency might have occurred after the initiation of Cushing's syndrome and in association with it.

Close investigation of the clinical course shows that the patient had felt severe general malaise and weight loss at around 40 years of age concomitant with the onset of amenorrhea. A few years later, the general malaise rapidly improved with the appearance of obesity and hypertension. If amenorrhea, general malaise and weight loss were the symptoms of isolated ACTH deficiency, we must support that isolated ACTH deficiency pre-existed Cushing's syndrome. General malaise would rapidly improve as the elevation of plasma cortisol by Cushing's syndrome. On the other hand, the possibility that isolated ACTH deficiency could be initiated after the onset of Cushing's syndrome cannot be denied completely. Consider the

existence of anti-pituitary antibody in the serum, it will be speculated that the autoimmune mechanism is the cause of this isolated ACTH deficiency. So it can be speculated that the deficiency might be aggravated from the so-called immune rebound phenomenon as a result of activation of the autoimmune mechanism by dose reduction of hydrocortisone replacement.

Concerning the treatment of this case, we should be aware of the probability of the remission of this isolated ACTH deficiency. We experienced another case of a pituitary antibody positive woman with isolated ACTH deficiency[13], who could be withdrawn from hydrocortisone supplement within 6 years. In the period of remission, the autoantibody to pituitary cell converted to negative. Another suggestive case of isolated ACTH deficiency which spontaneously remitted after a year of delivery[14] was reported. As considered above, it is necessary to trace the recovery of ACTH secretion regularly, prudently attempting hydrocortisone withdrawal as in the present case. Moreover, given such a case, we must be careful whether isolated ACTH deficiency might be concealed or not when dealing with withdrawal of hydrocortisone after surgery for Cushing's syndrome.

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