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A CASE OF OCCULT ECTOPIC CORTICOTROPIN (ACTH) SYNDROME MAITAINING REMISSION STATE OVER 4 YEARS AFTER BILATERAL ADRENALECTOMY

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Abstract: A long-lasting state of remission of over 4 years of occult ectopic corticotropin (ACTH) syndrome in a 68-year-old female is reported. She presented with general malaise, muscle atrophy and weakness of extremities, general petechiae and hypokalemia. Although ectopic ACTH syndrome was suspected due to marked hypercortisolism and ACTH elevation, the source of ACTH secretion could not detected by any diagnostic technique. Because of that effective suppression of plasma cortisol levels by torilostane, a 3 β-hydroxy-steroid-dehydrogenase inhibitor, could not obtained, so bilateral adrenalectomy was performed. After the operation, supplemental therapy of hydrocortisone and Florinef, 9 α-fluorohydrocortisone, was initiated and the plasma ACTH levels decreased gradually. At the 6th postoperative month, the levels of ACTH remained within the normal range and her general status markedly improved. At the 4th postoperative year, the plasma ACTH still maintained normal levels with no recurrence. Cases of occult ectopic ACTH syndrome which remain in remission for a long period after bilateral adrenalectomy are rare and interesting. Bilateral adrenalectomy may be the first choice of treatment for occult ectopic ACTH syndrome with the support of chemical therapy.

Index Terms

Ectopic corticotropin syndrome, ectopic ACTH syndrome, Cushing's syndrome, bilateral adrenalectomy

In ectopic ACTH syndrome, oat-cell carcinoma of lung[1], thymic tumor, pancreatic islet cell tumor[2], bronchial carcinoid[3,4] are the well known causes of this syndrome. Most such cases of ectopic ACTH syndrome are malignant tumor with poor prognosis due to the difficulty of complete extirpation of the tumor. For the control of excess ACTH-induced hypercortisolism, metyrapone[5,6], o, p'-DDD[7,8], aminoglutethimide[9], torilostane[10] and their combination therapy[7] have been used with some effectiveness. In recent reports, ketoconasol[11,12], an imidazole derivative drug, and long-acting somatostatin analog octreotide[13,14] had good response and some success to control ectopic ACTH secretion. Bilateral adrenalectomy is performed in cases of undetectable ACTH secretion, termed occult ectopic ACTH syndrome, or those resistant to chemotherapy[15]. We describe a patient with occult ectopic ACTH syndorome and discuss the mechanism of the normalization of ACTH serection after bilateral adrenalectomy.

METHODS

The concentration of 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, INCSTER Co., Stillwater, USA). The normal ranges for ACTH and cortisol are 4.4-48.0 pg/ml, 4.3-10.7 μg/dl, respectively. The intra- and inter-assay coefficients of variation of the IRMAs and RIAs were all within 10 %.

CASE REPORT

A 68-yr-old woman was admitted to our hospital for further evaluation of hypokalemia and elevation of plasma ACTH and cortisol. She had been treated at an associated hospital for diabetes mellitus from August 1991. During the treatment, general malaise and muscle weakness developed and progressed. Furthermore, hypokalemia (2.6 mEq/l), elevation of plasma ACTH (318 pg/ml) and cortisol(52.2 μg/dl) were found. She was sent to our hospital in April 1992. On physical examination, the patient presented with malaise, poor nutrition and gait disturbance wherein she could not walk without support due to muscle weakness. Height

Table 1. Laboratory datas on admission

Urine			
Protein	(−)		
glucose	(++)		
Peripheral Blood			
RBC	324×10^4	/mm³	
Ht	31.6	%	
Hb	10.6	g/dl	
WBC	9,600	/mm³	
Plt	21.3×10^4	/mm³	
Blood Chemistry			
T. Bil	0.6	mg/dl	
ZTT	1.7	KU	
ALP	326	IU/L	
GOT	19	IU/L	
GPT	17	IU/L	
LDH	682	IU/L	
ChE	401	IU/L	
LAP	62	IU/L	
γGTP	29	IU/L	
S-Amy	279	IU/L	
T Chol	268	mg/dl	
TG	141	mg/dl	
BUN	10	mg/dl	
Cr	0.4	mg/dl	
Na	140	mEq/L	
K	1.8	mEq/L	
Cl	90	mEq/L	
Fe	10	μg/dl	
Glucose	205	mg/dl	
CRP	(−)		

Tumor markers			
CEA	4.9	ng/ml	
CA 19-9	38.1	U/ml	
AFP	0.0	ng/ml	
SCC	1.2	ng/ml	
Basal Hormone values			
			(normal range)
ACTH	128.5	pgml	(4.4~48.0)
cortisol	56.4	μg/dl	(4.3~10.7)
GH	0.2	ng/ml	(<2.3)
TSH	1.6	μU/ml	(0.4~5.0)
T_3	65.4	ng/dl	(80~200)
T_4	5.2	μg/dl	(4.5~12.0)
PRA	1.44	ng/ml/hr	(0.5~2.0)
Aldosterone	41.5	pg/ml	(56.9~150.3)
IRI	14.9	μU/ml	(<5.0 μU/ml)
Glucagon	73	pg/ml	(40~140)
Gastrin	266.9	pg/ml	(30~150)
Carcitonin	52	pg/ml	(21.6~54.0)

was 152 cm ; weight, 39 Kg ; respiration, 14/min ; pulse, 105/min. On the skin of the extremities and chest, multiple petechiae and purpuric lesions were found. She was slightly moon faced with hyperemic skin. No pigmentation on skin was found. Severe muscle atrophy of the extremities was found with edema of the legs. No neurological abnormality was found.

1) Urinary, blood examination and basal hormone values (Table 1)

Glucosuria (++) was positive and proteinuria was negative. In peripheral blood, anemia was

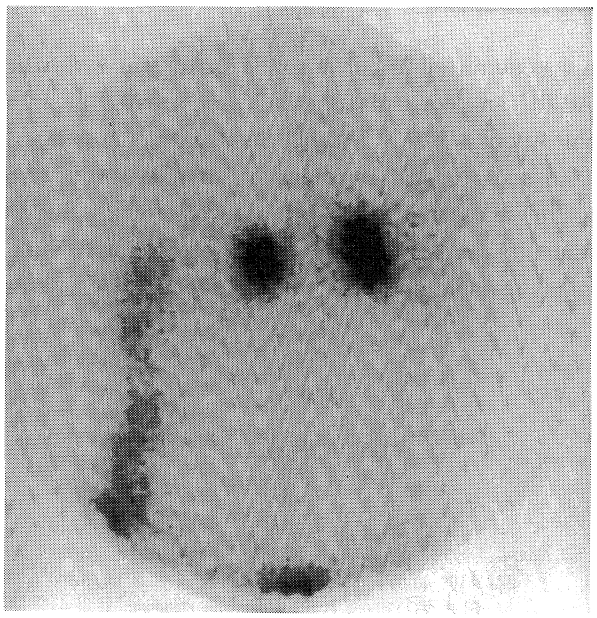

Fig. 1. Adrenal scintigram showed bilateral strong uptake of ^{123}I-Adosterol

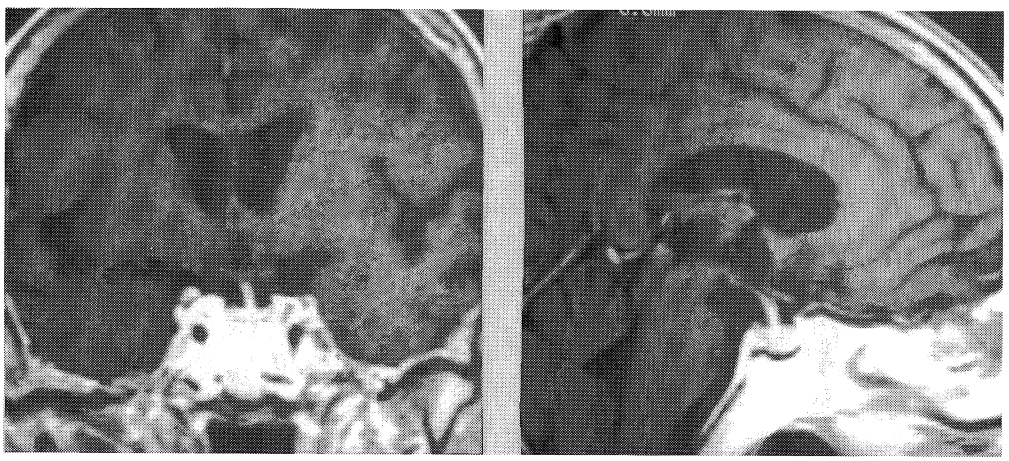

Fig. 2. MRI of pituitary and hypothalamic region showed no tumor. Slight shifting of pituitary stalk to the left side was found, but no mass legion was detected in the pituitary gland.

found (RBC $324\times10^4/\mu l$, Hb 10.6 g/dl). WBC was elevated slightly to $9,600/\mu l$. In blood chemistry, LDH and cholesterol were elevated. Serum K (1.8 mEq/l) was markedly low and fasting plasma glucose (205 mg/dl) was elevated. Among basal hormone values, ACTH and cortisol were elevated to 128.5 pg/ml and 56.4 μg/dl, respectively. Plasma renin activity (1.44 ng/ml/hr) and aldosterone (41.5 pg/ml) were in normal ranges. Tumor markers were entirely negative.

2) **Dexamethasone suppression test :** ACTH and cortisol were not suppressed by low dose (2 mg) Dexsamethasone suppression test. As hypokalemia was exacerbated during the administration of Dexamethasone, the high dose (8 mg) Dexamethasone suppression test was canceled.

3) **Adrenal scintigram (Fig. 1) :** High uptake of ^{123}-I adosterol was found in bilateral adrenal regions.

4) **Brain CT and MRI (Fig. 2) :** No tumor was found in the pituitary gland or other areas of

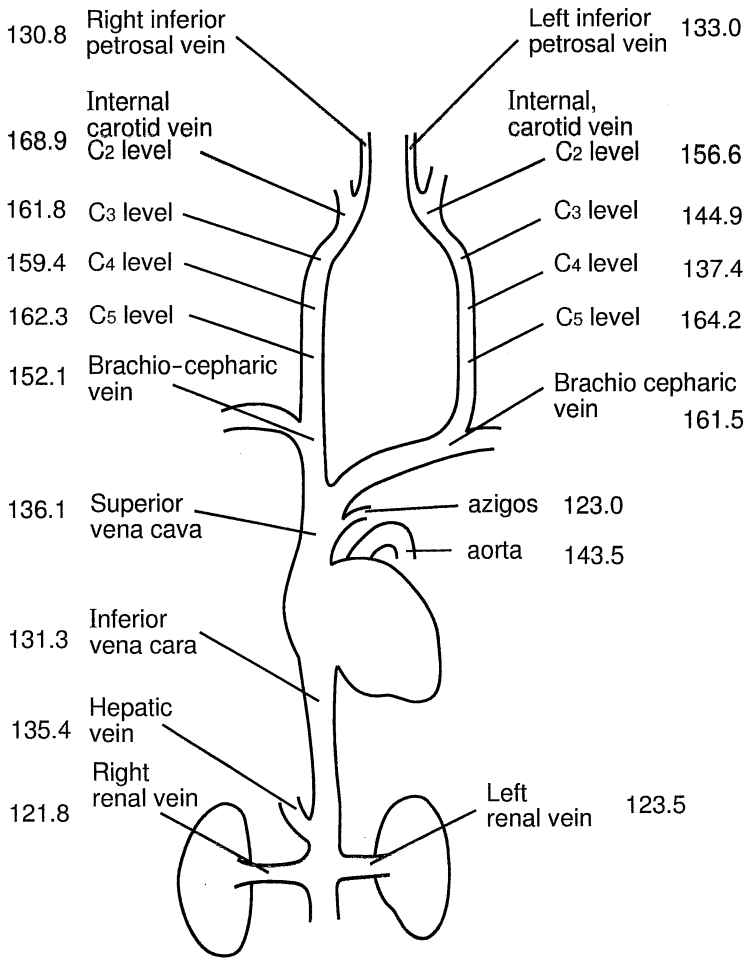

Fig. 3. Venous blood sampling from bilateral inferior petrosal vein to internal carotid vein showed no significantly high ACTH levels compared with other venous levels.

the brain. Slight shifting of pituitary stalk to the left side was found, but no mass lesion was detected in pituitary gland.

Considering these data, Cushing's disease was almost ruled out and ectopic ACTH syndrome was strongly suspected. We employed several imaging methods to detect any ectopic ACTH -secreting tumor.

5) Searching for ectopic ACTH secretion

Chest roentgenogram showed a small amount of bilateral pleural effusion and a localized diffuse shadow in the left lower lung field. Pleural fluid was examined but negative in cytology and bacterial analysis. The neck, chest, abdomen and pelvic region were examined by CT, with no tumor shadow being detected. Chest CT revealed pleural effusion in both pleural spaces and the atelectatic area in the left lower lobe. Bronchofiberscopy revealed no malignant findings in the atelectatic area. Fiberscopic examination of the upper alimentary tract and colon were negative. General Ga-scintigraphy showed no abnormal uptake.

6) Venous blood sampling (Fig. 3) : Venous blood sampling was performed by catheter from the bilateral inferior petrosal vein to the internal carotid vein and from some levels of the vena cava inferior. No significantly high level of ACTH was found at any level or branch of vein. The samples from upper levels of the bilateral carotid vein showed slightly higher ACTH levels compared to the inferior vena cava. Compared with the level of ACTH at the brachial vein, that of the inferior petrosal vein was not as high. No significant laterality was found in the levels of ACTH between the left and right inferior petrosal vein even under corticotropin releasing hormone (CRH) loading sampling (Table 2).

The above data indicate that rather than Cushing's disease, the diagnosis of ectopic ACTH syndrome with occult ACTH secretion was correct. As her general status worsened, torilostane administration at 480 mg/day was initiated. After the administration, the plasma cortisol levels descended to less than 30 μg/dl, but could not be lowered to levels within the normal range (Fig. 4). The ACTH level decreased to 58 pg/ml, accompanying the lowering of plasma cortisol. Although torilostane had some effect, it could not reduce the cortisol level under 25 μ/dl, so that hypokalemia and petechiae persisted. Bilateral adrenalectomy was performed on July, 30 th, 1992.

7) Histology of the extirpated adrenal gland (Fig. 5) : Neither tumor nor nodular change were found in either adrenal gland, but the cortical zone showed hypertrophy. ACTH and anti diuretic hormone (ADH) were both negative by PAP staining, using anti-ACTH and anti-ADH serum.

Table 2. CRH loading venous sampling

	Plasma ACTH level (pg/ml)			
	Bf.	2'	5'	15'
Brachial vein	118.0	127.4	128.0	130.0
Right inferior petrosal vein	136.6	137.0	116.9	119.8
Left inferior petrosal vein	134.8	106.8	108.8	120.8

8) **Clinical course after bilateral adrenalectomy (Fig. 6) :** After the bilateral adrenalectomy, hydrocortisone and Florinef were supplemented. Hypokalemia, petechiae and pleural effusion rapidly disappeared. By the 3rd postoperative month, she could walk without help. The postoperative plasma ACTH levels are presented in Fig. 6. The levels elevated transiently after surgery, but gradually lowered to normal levels under 50 pg/ml, finally remaining within the 20's pg/ml. After the first postoperative year, plasma ACTH remained at normal levels with no abnormality being found in any image examination. During the supplementation of hydrocortisone (30 mg/day) and Florinef (0.5 mg/day), CRH loading and Dexsamethasone suppression tests were performed. Plasma ACTH responded slightly to the CRH test and was not suppressed by Dexamethasone. These results indicated that the ectopic ACTH secretion still persisted. In fact, during the next 4 years of follow-up, the plasma ACTH levels remained within the normal range while CRH and Dexamethasone suppression test still gave the same results as above. The patient's general status markedly improved, and she was able to live a normal daily life.

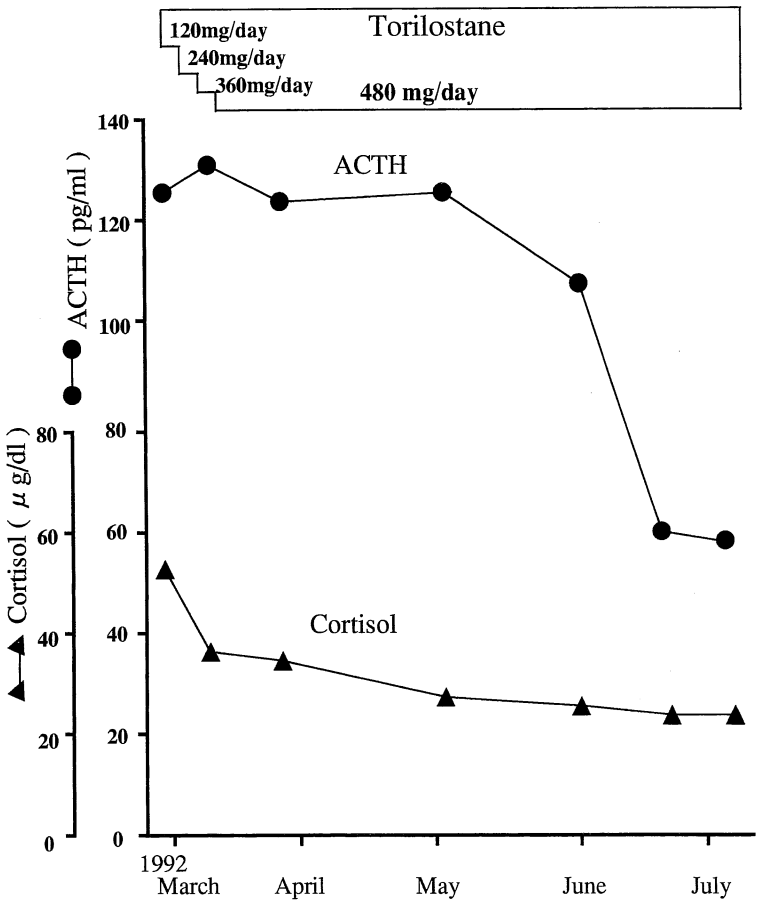

Fig. 4. Plasma ACTH and cortisol levels after Torilostane administration. The ACTH and cortisol levels lowered but could not reach the normal levels.

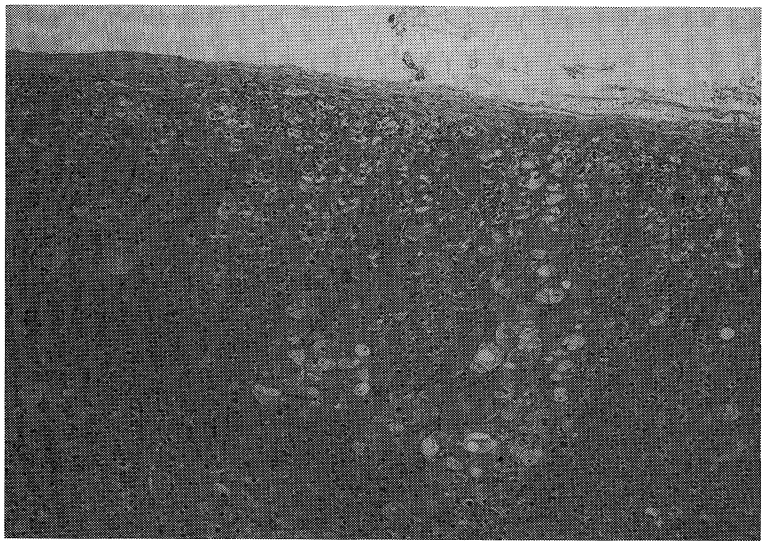

Fig. 5. Histology of the extirpated adrenal gland revealed no tumor, but only hypertrophy of the cortical zone.

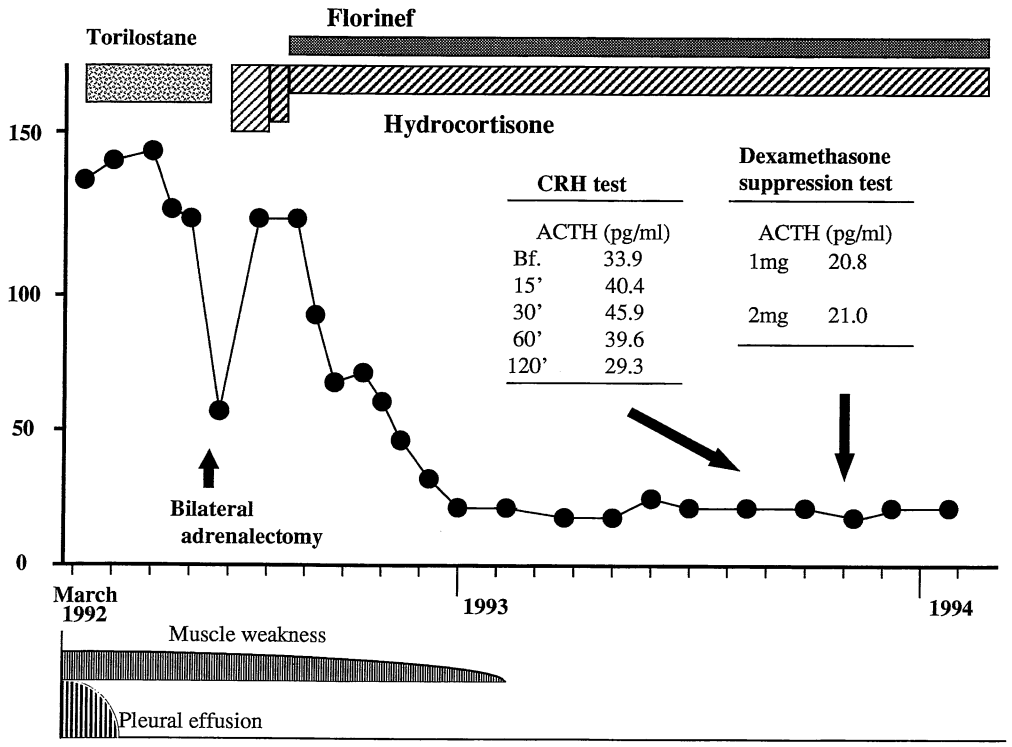

Fig. 6. Over the clinical course of bilateral adrenalectomy, normalization of ACTH levels were reached.

DISCUSSION

The diseases inducing ectopic ACTH syndrome are almost always malignant with poor prognosis. Pulmonary cancer of the oat cell type, bronchial carcinoid tumor and pancreatic islet cell carcinoma are well known examples of such malignant diseases. On the other hand, some cases induced from non-malignant disease[16] or inflammatory tissue[17] have also been reported. Other cases, the causes of which could not be clarified by any diagnostic examination, have been termed occult ectopic ACTH syndrome. These cases comprise about 12 % of ectopic ACTH syndrome cases[18]. Even if the case is occult, Torilostane, metopirone and Ketoconazol are usually used for the control of excess cortisol production. In a recent report, octreotide proved to be an effective control of ectopic ACTH secretion[13]. In another report, bilateral adrenalectomy was effective and safe in the management of various symptoms due to hypercortisolism[15].

Our case, presenting with severe malaise, muscle atrophy, spinal osteoporosis with fracture, edema, hypertension and hypokalemia, showed ACTH-dependent hypercortisolism which called for a differential diagnosis between Cushing's disease or ectopic ACTH syndrome. Neither pituitary tumor nor marked shifting of the pituitary stalk was found in CT or MRI examination. Even with the other diagnostic imaging methods, the origin of ACTH secretion could not be clarified. In chest roentgenogram, pleural effusion was found in the left side. In examination of the pleural fluid, the cytology was negative and the ACTH level of the fluid did not exceed that of the plasma levels. It was speculated that this pleural effusion may have been due to congestive heart failure induced by the overload of circulating plasma volume brought about by hypercortisolism. Furthermore, among the venous sampling, the ACTH levels of the upper carotid vein were somewhat higher than other samples. The thyroid gland, salivary gland and nasal sinus were negative in MRI examination. Some reports have revealed that the petrosal venous sampling under CRH loading [18-21] or high dose Dexamethasone loading[22] were useful for differentiating between Cushing's disease and ectopic ACTH syndrome. However, in our patient, neither elevation nor laterality of ACTH concentration was found by inferior petrosal venous sampling under CRH-loading. These data ruling out ACTH secretion of pituitary origin, the administration of torilostane was started. By this therapy alone, plasma cortisol was not lowered sufficiently. Although there are reports showing that the combination therapy with torilostane, metyrapone and op'-DDD was effective[7], such strong therapy was deemed not suitable for the present case. Given the above conditions, surgery was performed.

The two most probable causes for the spontaneous normalization of plasma ACTH concentration after bilateral adrenalectomy are speculated:

1. ACTH-producing tissue was contained in the extirpated adrenal glands.
2. Ectopic ACTH induced hypercortisolism had stimulated the ACTH-producing tissue, a vicious circle, but then atrophied after extirpation.

We examined the extirpated adrenal glands immuno-histochemically, using ACTH staining, with negative results. The second etiology gave a probability. However, 3 years after the adrenalectomy, the plasma ACTH was neither suppressed by the Dexamethasone suppression test nor did it respond to the CRH test, indicating persistent occult and ectopic ACTH secretion. Even after 4 years of follow-up, no ectopic ACTH-producing origin could be

detected. Concerning the therapeutic indication, bilateral adrenalectomy is recommended for the cases of occult ectopic ACTH syndrome. In support, Ziger et al.[15] found that bilateral adrenalectomy was a safe and efficacious treatment for ectopic ACTH syndrome. However, surgery must be performed before the general status becomes so poor that the patient cannot tolerate the operation. We conclude that bilateral adrenalectomy should be regarded as the first choice of treastment in occult ectopic ACTH syndrome because known chemotherapeutic regimens are unsatisfactory to suppress the ectopic ACTH secretion. Chemotherapy should be regarded as a supplemental means to control the high plasma levels of ACTH and cortisol before bilateral adrenalectomy.

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