

Long-term Remission of Cyclic Cushing's Disease that was Diagnosed and Treated Surgically in Non-active Phase

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Abstract. Cyclic Cushing's disease is a rare clinical entity that is defined as a periodic excessive production of adrenocorticotrophic hormone (ACTH) and cortisol. Only 42 cases with cyclic Cushing's disease have been reported in the literature. The diagnosis is very difficult because of the fluctuating secretion of ACTH and cortisol. We report a 78-year-old woman with a pituitary adenoma presenting with cyclic Cushing's disease. In the present case, several interesting issues are pointed out: 1) MRI study detected the presence of an adenoma and selective venous sampling in the cavernous sinus disclosed the hypersecretion of ACTH from a pituitary adenoma. These neuroimaging and endocrinological studies were helpful for the diagnosis, even in the remission phase. 2) The disease was in the long-term remission phase after transsphenoidal surgery despite the high recurrence rate in this clinical entity, although it recurred four years later. Even in the remission phase of cyclic Cushing's disease, meticulous endocrinological and neuroimaging examinations can reveal the presence of a pituitary adenoma, which should be treated surgically.

Key words: Cyclic Cushing's disease, ACTH, Cortisol, Pituitary adenoma

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CYCLIC Cushing's disease is a rare clinical entity that is defined by an excessive production of adrenocorticotrophic hormone (ACTH) and cortisol in a regular cycle ranging from a few days to several months. Thus far, only 42 cases with cyclic Cushing's disease have been reported in the literature [1–37]. This rare condition has distinctive endocrinological characteristics that are different from overt Cushing's disease without cyclicity: 1) no suppression of cortisol by high dose administration of dexamethasone [1–3, 9–12, 16, 25]; 2) blunted response of ACTH to an intravenous administration of corticotropin-releasing hormone (CRH) [15,

17, 21, 22]; and 3) suppression of ACTH by bromocriptine [17, 19, 21, 22, 28]. Nevertheless, the diagnosis and surgical treatment of cyclic Cushing's disease are difficult. In this paper, we report a patient presenting with cyclic Cushing's disease, and discuss the diagnostic and surgical difficulties of this disease, with review on the literature.

Case Report

A 78-year-old woman presented with hypertension since 1997. She also presented with pretibial edema since 1998. In April, 1999, hypopotassemia (K 2.2 mEq/l), depressive state and suicide attempt manifested, and she was admitted to a psychiatric hospital. In August, 1999, depressive state and pretibial edema spontaneously improved, and serum potassium con-

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Table 1. Endocrinological summary of the patient

	2000.2.			2000.4.			2000.6.		
		2 mg DEX	8 mg DEX		basal/ CRH	peak/ CRH		basal/ CRH	peak/ CRH
Urinary17-OHCS (3.4–12.0 mg/day)	51.3	38.5	20.7				7		
Urinary free cortisol (11.2–80.3 µg/day)	3029	1896	598				106.8–172.4		
plasma ACTH (7–56 pg/ml)	72	97	90	139–160.4	139	179.7	18.2–52.6	30	171.4
serum cortisol (4–18.3 µg/dl)	38.9	49.4	50	76–80	76	92	11.5–14.2	11.5	23.5
serum K (3.5–5.3 mEq/l)	1.7			3.7			4.4		
eosinocyte (0.0–7.0%)				0			0.8		
phase	active			active			remission		

	2000.8. postop	2000.9.	2001.2.					2004.11.
				basal/ CRH	peak/ CRH	O/N DEX 1 mg	O/N DEX 8 mg	
Urinary17-OHCS (3.4–12.0 mg/day)			4					
Urinary free cortisol (11.2–80.3 µg/day)			56.6					
plasma ACTH (7–56 pg/ml)	34.8		45.8	43.7	79	15.7	11.2	242
serum cortisol (4–18.3 µg/dl)	17.5	8.1		7.5	12.9	1.3	1.7	92.6
serum K (3.5–5.3 mEq/l)	4.2	3.8	4.3					1.2
eosinocyte (0.0–7.0%)	2.2	1.1	3.2					0
phase	remission	remission	remission					active

17-OHCS: 17-hydroxycorticosteroid

ACTH: adrenocorticotrophic hormone

DEX: dexamethasone

CRH: corticotropin-releasing hormone

centration was normalized (K 4.3 mEq/l). In February, 2000, depressive state, along with edema and hypokalemia (K 1.7 mEq/l), manifested again. Then the patient was admitted to Gengendo Kimitsu Hospital. As shown in Table 1, blood chemistry revealed elevated levels of plasma ACTH of 72 pg/ml (normal range: 7–56 pg/ml) and serum cortisol of 38.9 µg/dl (4–18.3 µg/dl). Urinary 17-hydroxycorticosteroid (17-OHCS) and free cortisol levels were 51.3 mg/day (3.4–12.0 mg/day) and 3029 µg/day (11.2–80.3 µg/day). These elevated values of urinary 17-OHCS and free cortisol were not suppressed to normal range by administration of 2 mg/day dexamethasone for 2 days or by 8 mg/day dexamethasone for 2 days. Magnetic resonance imaging (MRI) revealed a pituitary adenoma. Based on these endocrinological and neuroimaging examinations, the patient was suspected to have cyclic Cushing's disease, and referred to Teikyo University Chiba Medical Center in April, 2000. She had no habit of alcohol drinking.

Physical examination revealed thinning of skin and

edematous extremities, without characteristic Cushingoid features including central obesity and moon face. Blood chemical examination revealed elevated levels of plasma ACTH of 139–160.4 pg/ml and serum cortisol of 76–80.0 µg/dl. Percentage of eosinocyte (Eo) in white blood cell (WBC) count was 0%. Diurnal rhythm of ACTH and cortisol was lost. After CRH stimulation, basal/peak plasma ACTH and serum cortisol values were 139/179.7 pg/ml (30 min), and 76/92 µg/dl (60 min), respectively. The patient had pneumonia and urinary tract infection that was treated medically. In June, 2000, after CRH stimulation, basal/peak plasma ACTH and serum cortisol values were 30/171.4 pg/ml (30 min), and 11.5/23.5 µg/dl (60 min), respectively. Urinary 17-OHCS and free cortisol were 7 mg/day and 106.8–172.4 µg/day, which were remarkably reduced, compared with the values in February, 2000 (51.3 mg/day and 3029 µg/day). Plasma ACTH and serum cortisol levels were reduced to 18.2–52.6 pg/ml and 11.5–14.2 µg/dl. Serum potassium level was also normalized (K 3.7–4.4 mEq/l). Percentage

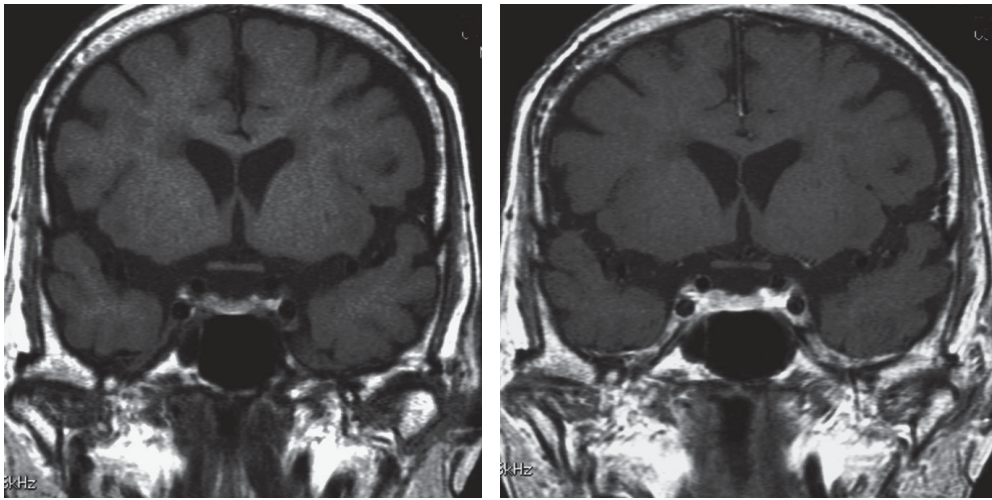


Fig. 1. T1-weighted MRI revealed a low signal intensity lesion (left) with less enhancement (right) in the right half of the pituitary gland, which suggested a pituitary adenoma (coronal section).

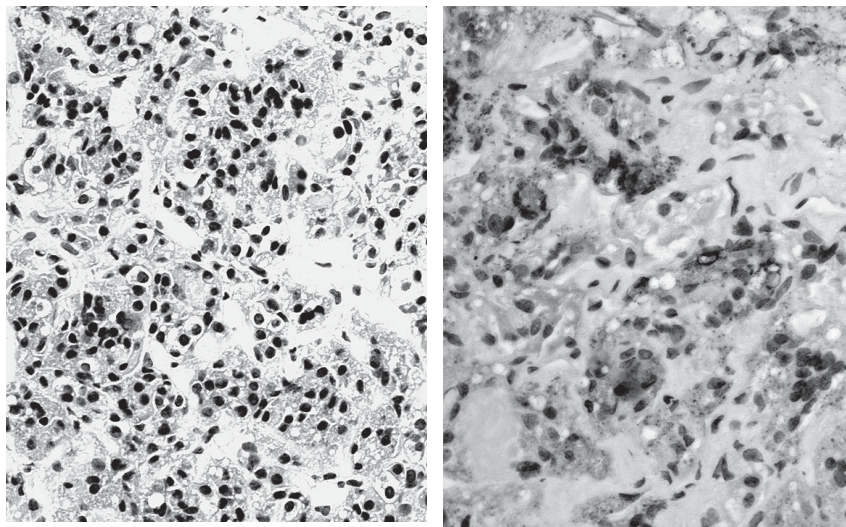


Fig. 2. Histopathological examination with hematoxylin-eosin staining confirmed the tumor as a chromophobe pituitary adenoma (original magnification $\times 200$, left). Immunohistochemical staining revealed ACTH-immunopositive cells (original magnification $\times 200$, right).

of Eo in WBC count was 0.8%. These endocrinological studies revealed the remarkable normalization of ACTH-cortisol axis. T1-weighted MRI disclosed a less enhanced lesion in the right half of the pituitary gland (Fig. 1), and selective venous sampling in the right cavernous sinus revealed high value of ACTH (440.5 pg/ml) compared with peripheral plasma ACTH level (37.1 pg/ml) (central/peripheral ratio 11.9).

Transsphenoidal surgery was carried out on August 24, 2000, and the tumor in the pituitary gland was removed. Histopathological examination with hematoxylin-eosin

staining confirmed the tumor as a chromophobe pituitary adenoma (Fig. 2-a), and immunohistochemical staining revealed ACTH-immunopositive cells (Fig. 2-b). Postoperative basal levels of plasma ACTH and serum cortisol were 34.8 pg/ml and 17.5 μ g/dl, respectively. Postoperative cortisol level was not suppressed but was within normal range, suggesting that the surgical procedure controlled hypersecretion of ACTH, but failed to extirpate the ACTH-secreting adenoma cells. Serum potassium level was 4.2 mEq/l, and percentage of Eo in WBC count was 2.2%. Other endocrinological

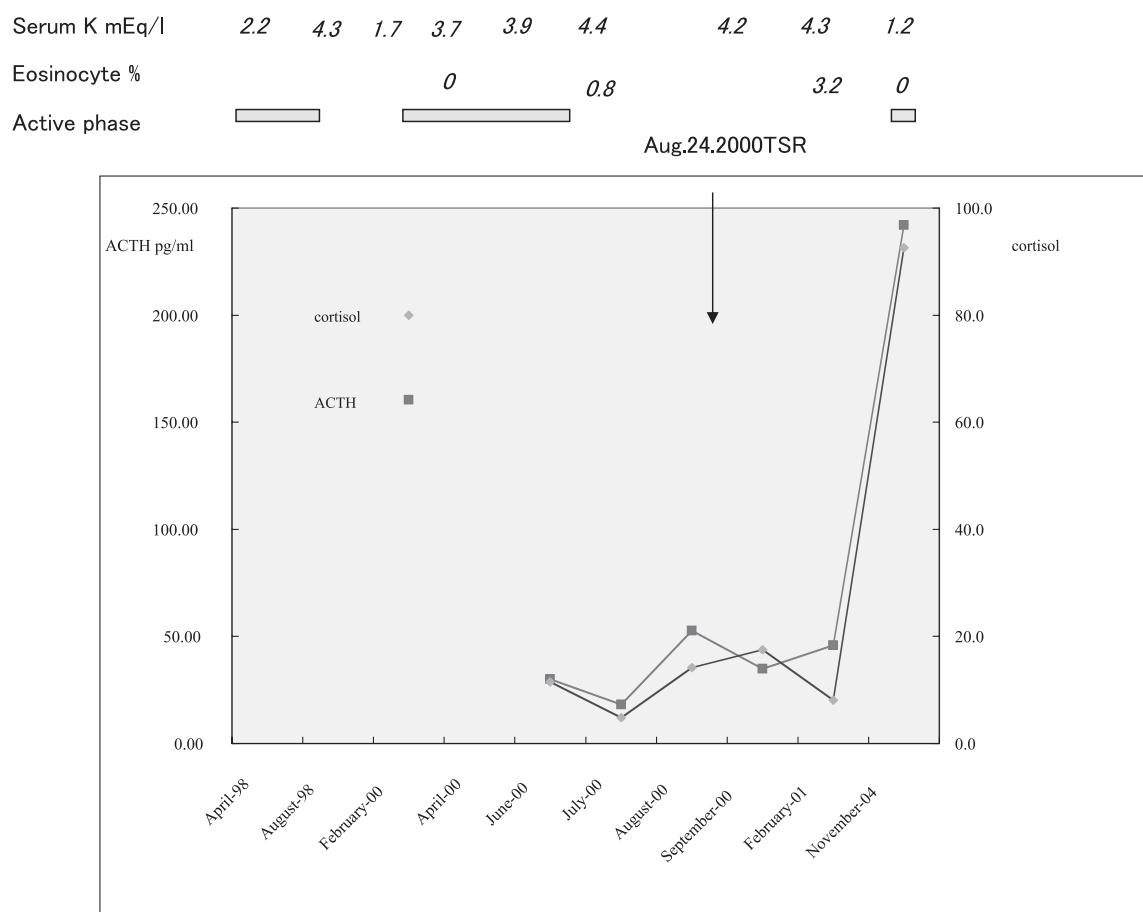


Fig. 3. Clinical course of the patient

studies including CRH or dexamethasone loading test and studies of diurnal rhythm of ACTH and cortisol were not performed in that postoperative period.

Repeated abnormal secretion of ACTH and cortisol, and repeated deterioration and improvement of clinical symptoms suggested the diagnosis of cyclic Cushing's disease.

In February, 2001, the patient was hospitalized for endocrinological evaluation. Plasma ACTH and serum cortisol levels were 45.8 pg/ml and 8.1 μg/dl, respectively. Urinary 17-OHCS and free cortisol were 4 mg/day and 56.6 μg/day. Serum potassium level was 4.3 mEq/l. Percentage of Eo in WBC count was 3.2%. Diurnal rhythm of ACTH and cortisol was observed. After CRH stimulation, basal/peak plasma ACTH and serum cortisol values were 43.7/79.0 pg/ml (15 min), and 7.5/12.9 μg/dl (30 min), respectively. Overnight dexamethasone test suppressed ACTH and cortisol levels to 15.7 pg/ml and 1.3 μg/dl (1 mg dexamethasone) and 11.2 pg/ml and 1.7 μg/dl (8 mg dexamethasone).

These results suggested that the patient was in remission phase of cyclic Cushing's disease.

However, in November 2004, the patient was hospitalized again with depressive state. Plasma ACTH and serum cortisol levels were remarkably elevated to be 242 pg/ml and 92.6 μg/dl, respectively. Serum potassium level was 1.2 mEq/l, and percentage of Eo in WBC count was 0%. MRI did not disclose the recurrence of pituitary adenoma. The patient died due to rectal ulcer and ensuing multiple organ failure. The clinical course of the patient is presented in Fig. 3.

Discussion

Cyclic Cushing's disease was first reported in 1973 by Brown *et al.* [1], and since then 42 patients with cyclic Cushing's disease have been reported in the literature [1–37]. The possible causes of periodicity of cortisol were reported to be infarcts [5], partial necrosis

[8] or calcification [12] of the tumor, or patient stress [15]; however, the precise mechanism is still unclear. The fluctuation of cortisol and ACTH secretion makes it difficult to establish the diagnosis of cyclic Cushing's disease, especially in the remission phase. Transsphenoidal surgery is not effective in the treatment of this disease [3, 14], and the cure rate is only 25% and recurrence rate is 63% [28].

A typical cyclic Cushing's disease has characteristic endocrinological features: 1) serum cortisol is not suppressed by high dose administration of dexamethasone [1–3, 9–12, 16, 25]; 2) plasma ACTH elevation is not blunted by an intravenous administration of CRH [15, 17, 21, 22]. These endocrinological features were observed also in the present case. The percentage of Eo in WBC count correlated well with the activity of the disease.

In the 42 reported cases of cyclic Cushing's disease, neuroimaging studies were carried out in 32 (76.2%) cases. In these 32 cases, neuroimaging studies including computed tomography (CT) scan or MRI revealed the presence of an adenoma in 14 (43.8%) cases. In 17 cases with MRI studies, an adenoma was identified in 8 (47.1%) cases. Therefore, even the most sophisticated neuroimaging studies can only disclose the presence of a pituitary adenoma in less than half of patients with cyclic Cushing's disease. The alteration of the tumor size between the active and remission phases has not been reported in the literature. Moreover, selective venous sampling was carried out in 10 cases out of the 42 reported cases. In 6 (60%) cases, the positive C/P ratio of ACTH was observed. Among these 6 cases,

only 1 patient had the positive C/P ratio of ACTH in the remission phase of cyclic Cushing's disease. In addition, in 2 cases with active phase of cyclic Cushing's disease, positive findings were not obtained in selective venous sampling study of ACTH. Thus, in selective venous sampling study of ACTH, the successful identification of ACTH production from a pituitary adenoma with cyclic Cushing's disease is a very rare event.

The present case included very interesting and significant issues of endocrinological and neuroimaging studies. First, MRI study detected the presence of an adenoma, and secondly, selective venous sampling in the cavernous sinus disclosed the hypersecretion of ACTH even in the remission phase. These neuroimaging and endocrinological studies were helpful for the diagnosis.

Another interesting issue is noted in the present case: the disease was in the long-term remission phase after transsphenoidal surgery, although in general the recurrence rate is high in this clinical entity. The patient was in the remission phase for nearly 4 years and 3 months postoperatively. It is difficult to determine whether the long-term remission is due to successful surgery or is merely a prolongation of remission period; however, this long postsurgical period of remission is noteworthy.

In conclusion, even in the remission phase of cyclic Cushing's disease, meticulous endocrinological and neuroimaging examinations can disclose the presence of a pituitary adenoma, which is worth being treated surgically.

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