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Periodic Secretion of Adrenocorticotropin in a Patient with Cushing's Disease Manifested during Pregnancy

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Abstract. We report the case of 19-year-old woman with cyclical Cushing's disease, in whom plasma adrenocorticotropin (ACTH) was secreted periodically after her first pregnancy. Since the 33rd week of pregnancy, hypertension and proteinuria became clinically remarkable. She gave normal birth at 36th week of pregnancy; however she continued to gain body weight even after delivery and developed typical Cushingoid features. Her ACTH secretion lacked normal daily fluctuation but exhibited periodic change during 1-year observation, showing 119 pg/ml, 34.6 pg/ml and 115 pg/ml at the 4th, 7th and 13th months after delivery. Plasma ACTH levels were increased by corticotropin releasing hormone and metyrapone, while low-dose dexamethasone suppressed cortisol secretion. Gel filtration analysis of the patient's plasma detected big ACTH molecules being eluted with a peak of authentic 1–39 ACTH. Cranial magnetic resonance imaging revealed a 1-cm pituitary mass in right cavernous sinus. The pituitary tumor was removed by transsphenoidal surgery at 13th month after delivery and was pathologically compatible with ACTH-producing pituitary adenoma by immunohistochemistry. This case includes clinically rare subsets of Cushing's syndrome showing periodic ACTH secretion and aberrant ACTH molecules.

Key words: Adrenocorticotropin (ACTH), Big ACTH, Cyclical Cushing's syndrome, Gel filtration analysis, Pituitary adenoma, Pregnancy

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IN patients with overt Cushing's syndrome, pituitary gonadotropin secretion is usually suppressed by excess of adrenocortical steroids including cortisol and androgen, which leads to anovulation and abnormal menstruation [1]. Nevertheless, pregnancy can occur on rare occasions in less active Cushing's syndrome and, in these cases, the symptoms seem to be obscure because either condition can be associated with such Cushingoid features as centrally distributed obesity, striae cutis, general fatigue, systemic edema, glucose intolerance, hypertension and proteinuria.

Cushing's disease is caused by hypercortisolism due to chronic overproduction of adrenocorticotropin (ACTH) from pituitary corticotropinoma. In general, Cushing's disease is the most common cause of Cushing's syndrome. Meanwhile, among the patients who developed Cushing's syndrome during pregnancy, approximately half of the etiology was reported to be adrenal adenomas, 30% was due to adrenal hyperplasia related to Cushing's disease, and the remaining 10% was caused by adrenal carcinomas and rarely by ectopic ACTH syndrome [2].

We here report an interesting case of Cushing's

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disease caused by ACTH-producing pituitary adenoma manifested during pregnancy, in which serum cortisol levels fluctuated and Cushingoid features changed during the 1-year observation period. Although a subgroup of Cushing's disease exhibits periodic fluctuations in ACTH and/or cortisol secretion [3], the underlying mechanism of hormonal cyclicity remains unknown.

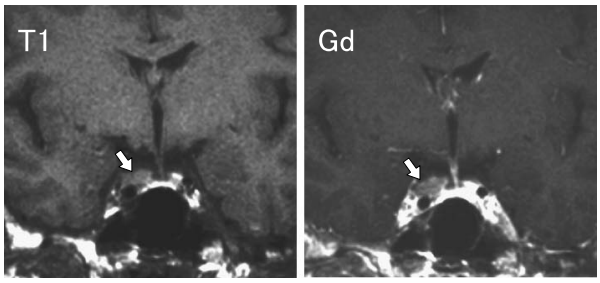

Fig. 1. MRI findings of pituitary tumor. Coronal T1-images with gadolinium (Gd) enhancement are shown before transsphenoidal surgery (indicated by arrows).

Case Report

A 19-year-old Japanese woman, who presented hypertension, obesity and proteinuria during her first pregnancy, was referred to our hospital after delivery. Her past medical history was negative and menstrual cycle was normal until pregnancy. Since the 33th week of pregnancy, she developed hypertension (150–170/86–90 mmHg), systemic edema and excessive weight gain (13 kg during pregnancy). She delivered a healthy boy weighing 3,250 g at 36th week of pregnancy. But she still gained body weight up to 3.5 kg even after delivery, and developed Cushingoid features including moon face, facial acne, buffalo hump, truncal obesity, pretibial edema, and striae cutis purpura. A pituitary tumor in the sella turcica was detected by cranial magnetic resonance imaging (MRI) after delivery (Fig. 1), although her endocrine condition was not examined before and during pregnancy.

Four months after delivery, plasma ACTH and serum cortisol levels were found to be high at 119 pg/ml and 39.6 μg/dl, respectively (Fig. 2). Six months after delivery, circulating ACTH and cortisol levels were spontaneously reduced to 53.9 pg/ml and 13.7 μg/dl, respectively. Although no circadian fluctuation of ACTH or cortisol was observed (Fig. 3A), dexamethasone (1 mg, overnight method) suppressed cortisol secretion by 81%. At that time, urinary excretion of free cortisol was rather lower (<50 μg/day), and 17-ketosteroid (4.8 to 7.9 mg/day, normal: 2.4–11) and 17-hydroxycorticosteroid (5.9 to 8.1 mg/day, normal: 2.2–7.3) levels were within normal range. Metyrapone (1.5 g *po.*; Fig. 3B) or corticotropin releasing hormone (CRH, 100 μg *iv.*; Fig. 3C) significantly increased plasma ACTH levels (2- and 3-fold increase by metyrapone and CRH, respectively). In accordance with the decrease in ACTH and cortisol, her body

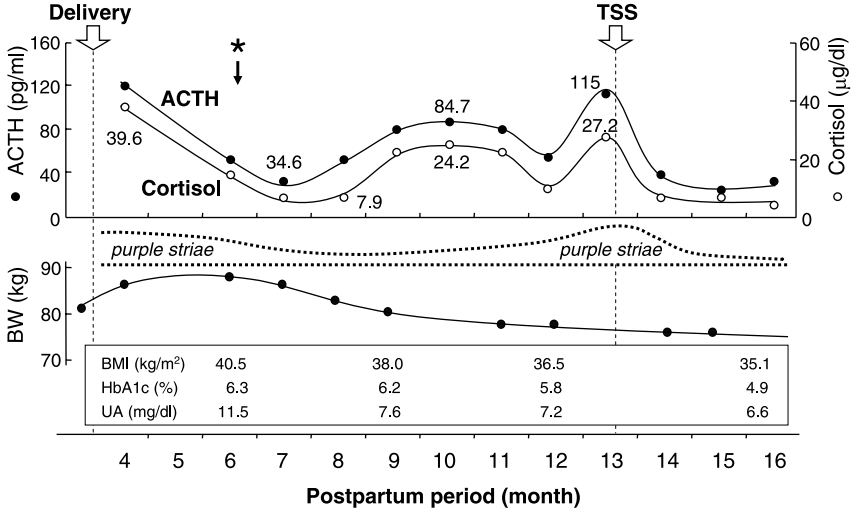

Fig. 2. Clinical course of the present case. TSS, transsphenoidal surgery. BMI, body mass index (kg/m^2); BW, body weight; UA, uric acid in serum; *arrow, at the time point when daily profile (Fig. 3A), metyrapone (Fig. 3B) and preoperative CRH tests (Fig. 3C) were performed.

weight and BMI gradually reduced and purple striae became faint during observation (see Fig. 2). However, at 10 months after delivery, the levels of ACTH and cortisol elevated once again and the pigmentation of her striae became remarkable. Therefore, transsphenoidal surgery was performed at 13th month after delivery and approximately 80% of the tumor was successfully removed. Histologically the resected tumor was pituitary adenoma and its ACTH production was proven by immunohistochemistry (Fig. 4).

After surgery, the levels of ACTH and cortisol were normalized and ACTH response to CRH was reduced (2-fold increase) (Fig. 3C). Postoperative cortisol secretion was also suppressed by 76% by 1 mg dexamethasone as shown in the preoperative test. Symptoms of Cushing's syndrome including purple striae, glucose intolerance, obesity and the hyperuricemia gradually ameliorated and her menstruation resumed (Fig. 2). After surgery, the effects of dopamine agonists and somatostatin analogue on ACTH secretion from the remnant adenoma were evaluated. Bromocriptine (2.5 mg *po*.) and octreotide (100 μg *sc*.) only induced 16% and 25% reduction of plasma ACTH levels, respectively, but induced 40% and 35% reduction of serum cortisol levels, respectively. Effect of a long-acting dopamine agonist cabergoline (0.25 mg/week *po*.) was also tested and resulted in only 18% and 21% reduction of ACTH and cortisol levels, respectively, after 4-week treatment. All the ACTH data reported above were measured by ACTH IRMA Yuka kit (Mitsubishi Chemical, Tokyo, Japan).

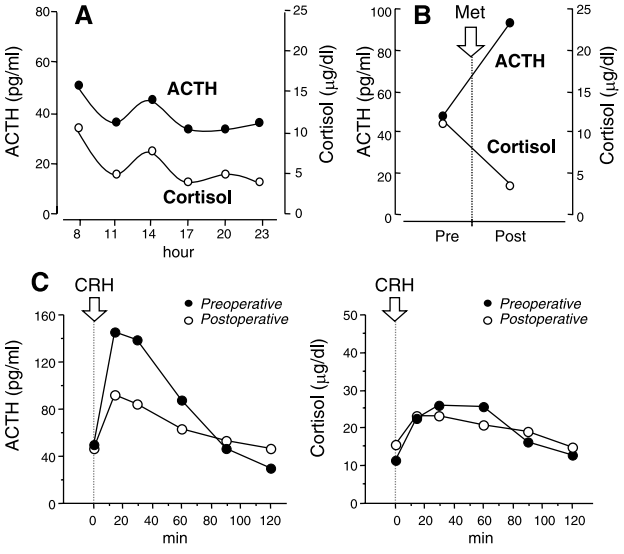

Fig. 3. A) Daily profile of ACTH and cortisol levels before surgery. B) Metyrapone (Met; 1.5 g) provocation test before surgery. C) CRH (100 μg) provocation test before and after surgery.

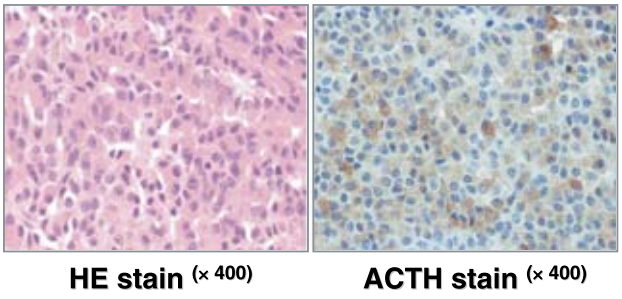

Fig. 4. Pathological findings of the resected pituitary tumor. Hematoxylin-eosin (HE) staining, × 400; and immunohistochemisty using anti-ACTH antibody, × 400.

Analysis of preoperative plasma ACTH by gel chromatography

Molecular analysis of circulating ACTH was performed by gel chromatography as previously reported [4, 5]. Briefly, the plasma sample was extracted using SEP-PAK C_{18} cartridge (Waters, Milford, MA). The plasma elutant (3 ml) was lyophilized, diluted with 200 μl of 1% formic acid and applied to a Sephadex G-75 column (0.9 × 45 cm; Amersham-Pharmacia Biotech, Piscataway, NJ), and then eluted with 1% formic

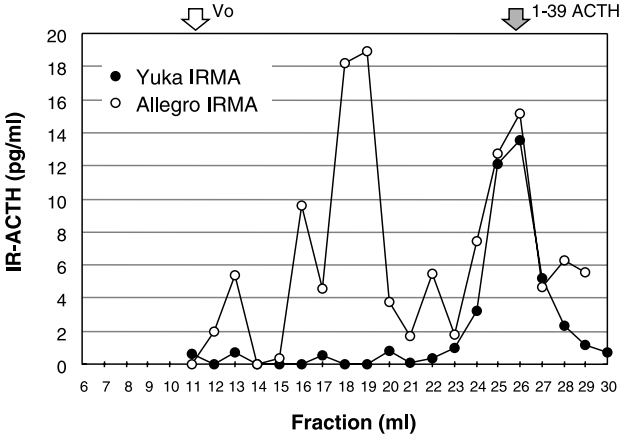

Fig. 5. Gel (Sephadex G-75, 0.9 × 45 cm) filtration analysis of preoperative plasma ACTH. Immunoreactive ACTH (IR-ACTH) concentration was determined by the IRMA methods using ACTH IRMA Yuka kit (Mitsubishi) and Allegro ACTH kit (Nihon Medi-Physics). Vo, void volume.

acid. After each 2 ml-fraction was fractionated and lyophilized, the ACTH concentration of each fraction was determined by two different immunoradiometric assays (IRMA); ACTH IRMA Yuka kit (using antibodies against 1–24 ACTH and 18–39 ACTH; Mitsubishi Chemical) that detected only a main peak of 1–39 ACTH; and Nichols Allegro ACTH kit (using antibodies against 1–17 ACTH and 34–39 ACTH; Nihon Medi-Physics, Tokyo, Japan) that mainly detected intermediate forms of ACTH molecules in addition to the big form and authentic 1–39 ACTH (Fig. 5).

Discussion

Thirty-two cases of Cushing's disease associated with pregnancy have been reported to date in the literature. Among the 43 births derived from these cases, 33 (77%) babies were found to be healthy, while the other 10 births included 4 cases of spontaneous abortion [6–8], 3 cases of technical abortion [8–10], 2 stillbirths [7, 11] and an early neonatal death due to extreme prematurity [12]. In general, premature labor occurs in more than half of the women with Cushing's syndrome regardless of the etiology [13]. This is possibly due to the passage of cortisol across the placenta and the subsequent suppression of the fetal adrenal function [14].

In the process of normal pregnancy, serum cortisol elevation occurs due to overproduction of cortisol binding globulin and urinary excretion of free cortisol can be increased [15]. Therefore, the laboratory evaluation of Cushing's syndrome during pregnancy is complicated. One of the most helpful means to distinguish Cushing's syndrome from hypercortisolism of normal pregnancy is to uncover loss of normal circadian variation in increased cortisol levels [15]. Furthermore, Ross *et al.* reported the significance of exaggerated ACTH response to CRH in a pregnant woman with Cushing's disease [16]. Unfortunately we could not assess the endocrine condition of our patient before delivery; however, the combination of CRH test and daily profile of circulating ACTH and cortisol would have been a safe and beneficial method for the early recognition of Cushing's syndrome.

Medication for Cushing's disease during pregnancy seems not to be very effective, although we cannot make a fair comparison of the degree of severity among the cases reported previously. A few reports document the efficacy of treatment with metyrapone [12]. Ketoconazole was given to two patients with complications of intrauterine growth retardation, but no malformations or other perinatal disorders were reported [17]. Although the experience of other drugs, such as aminoglutethimide [18], mitotane [10, 19], bromocriptine [9] and cyproheptadine [20–24], was also reported, aminoglutethimide and mitotane should be avoided as much as possible because of their potential toxicity to fetus. Transsphenoidal surgery of pituitary ACTH-secreting adenoma was carried out successfully in five patients during pregnancy [11, 16, 25–27]. Even radiation therapy was performed in a case of Cushing's disease during pregnancy [6]. Since many of the serious complications including hypertension, gestational diabetes and pulmonary edema can progress in Cushing's pregnancies, clinical vigilance is always necessary to maintain normal pregnancy. Based on a review of the literature, conservative management is most likely a prudent course in the milder cases [28–30]; nevertheless, it is worthy noting that premature onset of labor occurs quite frequently [31].

The clinical presentation of cyclical Cushing is extremely variable; namely, the cycles of excessive cortisol production can range from several weeks to several months, while the inactive phase can last from 1 or 2 months to several years [32]. The neuroendocrine mechanism underlying the periodicity of cortisol overproduction is still poorly understood. One of the explanations for this variability, at least in cyclical pituitary tumors, is the cyclical changes in central dopaminergic tone as a trigger for periodic ACTH secretion [33]. In our case, ACTH and cortisol levels were mildly decreased in response to dopamine agonists bromocriptine and cabergoline. The change of sensitivity for ACTH secretion in response to dopamine could be involved in the long-term cyclicity of ACTH secretion.

In the present case, it was revealed that both the high molecular-weight ACTH as well as the authentic 1–39 ACTH were present in the preoperative plasma by gel-filtration analysis. However, we cannot determine the amount of big ACTH and its ratio to 1–39 ACTH since we could not assess the recovery yield of the SEP-PAK C_{18} extraction. It is possible that the extraction process of SEP-PAK might have partially voided the big ACTH molecules in the plasma. Thus far, there has been no report regarding aberrant ACTH production in Cushing's disease associated with pregnancy, hence the clinical relevance of big ACTH molecules to cyclical Cushing's disease is still uncertain. However, it is

reasonable to assume that authentic ACTH secretion must have been relatively low at least until late pregnancy period. If so, the cyclic fluctuation and the presence of aberrant, possibly inactive, ACTH molecules could be favorable to induction and maintenance of normal pregnancy even under the pathological state of Cushing's syndrome.

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