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【 CASE REPORT 】

Oral Contraceptive Disturbed the Recovery of the Adrenal Function after Adrenalectomy in Cushing Syndrome

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Abstract:
Estrogen is known to increase exogenous corticosteroid levels. In this case, a 27-year-old Japanese woman was referred to our hospital for examination of an adrenal tumor and was diagnosed with Cushing syndrome. Resection of the tumor resulted in secondary adrenal insufficiency. She also developed microcytic anemia due to hypermenorrhea, which was masked by Cushing syndrome. An oral contraceptive was administered for the treatment of hypermenorrhea, but this led to a marked increase in serum cortisol and the reduction of plasma adenocorticotropic hormone, disturbing the recovery of the adrenal function. Attention is required when oral contraceptives are used to treat hypermenorrhea masked by Cushing syndrome.

Key words: adrenal Cushing syndrome, oral contraceptives, secondary adrenal insufficiency

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Introduction

If patients originally have hypermenorrhea, it may be masked by Cushing syndrome, which causes amenorrhea. In such cases, the masked hypermenorrhea may become apparent when hypercortisolism is cured. While oral contraceptives are generally used for prevention of hypermenorrhea, the administration of estrogen is known to increase endogenous or exogenous corticosteroids (1-6).

We herein present a case in which the recovery of the adrenal function was disturbed by oral contraceptive use after adrenalectomy for Cushing syndrome. Attention is required when oral contraceptives are used to treat hypermenorrhea masked by Cushing syndrome.

Case Report

A 27-year-old Japanese woman with an adrenal tumor was referred to our hospital for an endocrinological assessment. One year previously, her blood pressure had been 200/100 mmHg and treatment with amlodipine (5 mg per day) was initiated. Since then, she noticed general fatigue, moon face, red striae, acne and menstrual irregularity. Abdominal MRI revealed right adrenal mass of 3 cm in diameter, which was isointense to liver on T2-weighted sequences. On abdominal CT, the tumor was homogenous and exhibited low attenuation values (2.3 HU). On admission, the plasma adenocorticotropic hormone (ACTH) was <1.0 pg/mL and the serum cortisol level was 23.6 μg/dL. The serum potassium level was 3.2 mEq/L. The urinary cortisol level was 150.8 μg/day. The serum cortisol level after a 1-mg dexamethasone suppression test (DST) was 23.7 μg/dL and the midnight serum cortisol level was 20.8 μg/dL. The renin-aldosterone ratio and urinary catecholamine levels were within the normal range. She was diagnosed with adrenal Cushing syndrome. Hypercortisolism was managed by block and replacement therapy using metyrapone (1,500 mg per day) and hydrocortisone (15-20 mg per day) for three months. Then the tumor was laparoscopically resected and was histologically diagnosed as adrenal cortical adenoma.

After resection of the tumor, she developed secondary adrenal insufficiency and was treated with oral hydrocortisone. The time course of her adrenal function after adrenalectomy is shown in Figure. At all points, blood samples were collected before 10 AM without the morning dose of hydrocortisone. At all points, except for 15 months after adrenalectomy, hydrocortisone was administered in the evening on the

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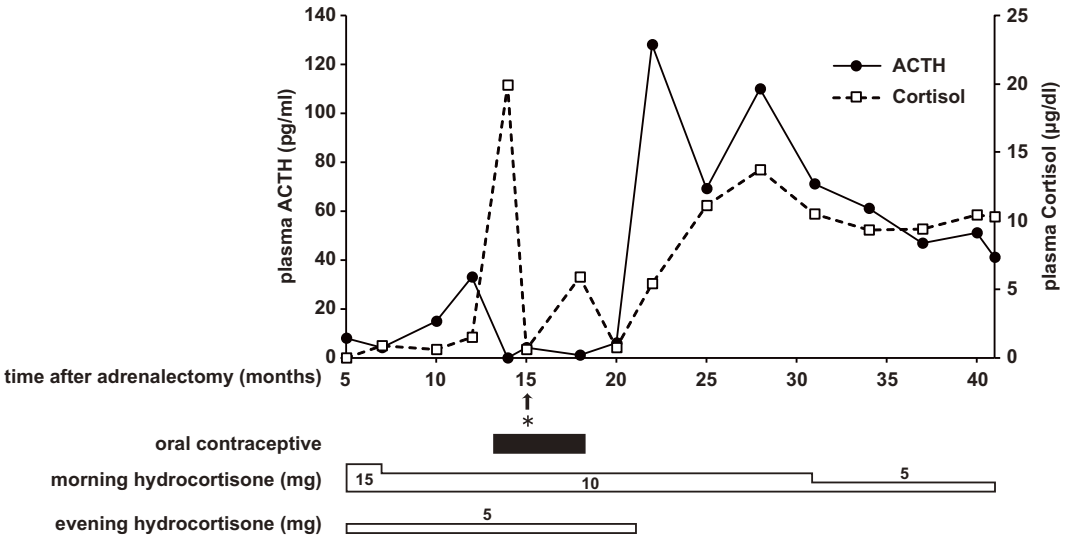

Figure. **The time course of the plasma ACTH and serum cortisol levels after adrenalectomy. From 13 to 18 months after adrenalectomy, an oral contraceptive was administered. Blood was collected before 10 a.m., without the administration of the morning dose of hydrocortisone. The evening dose of hydrocortisone was administered on the day before blood collection at every point, except for 15 months after adrenalectomy, when the evening dose of hydrocortisone was skipped the day before blood collection (*).**

day before blood collection. From 5 to 12 months after adrenalectomy, her plasma ACTH and serum cortisol levels gradually recovered to 33 pg/mL and 1.5 μg/dL, respectively. Although her hemoglobin (Hb) level was normal (12.3 g/dL) before adrenalectomy, she had microcytic anemia (Hb 10.2 g/dL and mean cell volume 78.8 fL) at that time, most likely due to hypermenorrhea after adrenalectomy. One month later (13 months after adrenalectomy), she consulted a gynecologist and was treated with Yaz® [Drospirenone (3 mg per day) and ethinyl estradiol (0.02 mg per day)] for hypermenorrhea. At the next visit (14 months after adrenalectomy), her serum cortisol was markedly elevated to 19.9 μg/dL, whereas the plasma ACTH level dropped to <1 pg/mL. Her anemia normalized. One month later (15 months after adrenalectomy), when she skipped the evening dose of hydrocortisone on the day before blood collection, her serum cortisol level was reasonably low at 0.6 μg/dL. Three months later (18 months after adrenalectomy) when the evening dose of hydrocortisone was administered the day before blood collection, her serum cortisol was again found to be high (5.9 μg/dL) whereas her plasma ACTH level was suppressed to 1 pg/ml. As oral contraceptives are reported to increase circulating free cortisol levels after exogenous hydrocortisone administration (6), we suspected that Yaz® might have impaired the disappearance of the evening dose of hydrocortisone, and the administration of Yaz® was stopped. Two months later (20 months after adrenalectomy), her serum cortisol was reasonably low (0.7 μg/dL) and her plasma ACTH level had slightly recovered to 6 pg/mL. To facilitate the recovery of the adrenal function, the evening dose of hydrocortisone was stopped and her plasma cortisol and ACTH levels were gradually normalized until 41 months after adrenalectomy, although a rapid ACTH test indicated partial impairment of the adrenal function (serum cortisol, 12.2 μg/dL) at 31 months after adrenalectomy.

Discussion

While the recovery of the adrenal function from secondary adrenal insufficiency requires appropriate oral hydrocortisone dosing, various studies have demonstrated the effects of estrogen on circulating corticosteroid levels. Even low-dose estrogen increases the endogenous total and free cortisol levels (1-4, 7) and reduces the plasma ACTH level, possibly through a negative feedback mechanism (7, 8). Similarly, the action of exogenous hydrocortisone is enhanced by relatively high-dose estrogen (approximately equivalent to 15-120 mg of diethylstilbestrol) (5), but low-dose oral contraceptives also increase circulating free cortisol levels after exogenous hydrocortisone administration (6). These effects of estrogen on free cortisol were considered to be mediated by the concomitant increase in hepatic corticosteroid-binding globulin (CBG) synthesis (1-4). CBG is the main reservoir of cortisol in the human body, binding 70-80% of total cortisol. The CBG-bound cortisol is protected from disappearance in the blood, which results in increased free cortisol, as well as the increase in the total cortisol concentration and the ratio of total to free cortisol (9, 10).

In this case, the patient's original hypermenorrhea was concealed by amenorrhea in Cushing syndrome. With the cure of Cushing syndrome, the masked hypermenorrhea became apparent and was treated with an oral contraceptive. With the constant dose of hydrocortisone, the oral contra-

ceptive increased the total (and possibly free) serum cortisol levels and suppressed the plasma ACTH level, probably disturbing the recovery of the adrenal function. In fact, the adrenal function was still partially impaired at 31 months after adrenalectomy, which is longer than one year, which is the average time to recovery from adrenal Cushing's syndrome after adrenalectomy (11). These hypotheses would have been verified by the measurement of CBG during and after oral contraceptive treatment. Instead of oral contraceptives, oral progestin may be considered for the treatment of hypermenorrhea, as progesterone has little effect on the metabolism of cortisol (12). Clinicians should be careful of this potential pitfall in the management of secondary adrenal insufficiency after Cushing syndrome.

The authors state that they have no Conflict of Interest (COI).

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