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A Rare Case of Placental Abruption and Postpartum Compression Fractures in Pregnancy With Cushing Syndrome

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Abstract

Cushing syndrome (CS) is a disorder rarely found during pregnancy. Patients with CS usually receive treatment before pregnancy. In addition, hypercortisolism suppresses gonadotropins, leading to amenorrhea or irregular menstruation. Therefore, few reports have described cases of pregnancy with untreated CS. Here, we observed the changes in the cortisol level of a 38-year-old woman with adrenal CS before and throughout pregnancy and delivery. She also had primary aldosteronism, and we were able to follow her plasma aldosterone levels. Her symptoms of CS before pregnancy were submandibular acne and irregular menstruation, but after conception, "moon face" and fatigue appeared. Laboratory tests also revealed impaired glucose tolerance, hypokalemia, lymphocytopenia, and increased urinary free cortisol levels. After administration of metyrapone to ameliorate her general condition, laparoscopic adrenalectomy was performed in the nineteenth week of pregnancy. After the operation, the patient's symptoms improved, and the cortisol level was maintained with hydrocortisone supplementation. The patient's plasma aldosterone level and blood pressure did not deteriorate throughout the course. However, the delivery was complicated by placental abruption. One month after delivery, the mother presented with compression fractures. We review the literature and discuss the treatment and complications of pregnancy with CS.

Key Words: pregnancy, placental abruption, compression fracture, Cushing syndrome, primary aldosteronism

Abbreviations: ACTH, adrenocorticotropic hormone; DVT, deep venous thrombosis; GDM, gestational diabetes mellitus; MRI, magnetic resonance imaging; PA, primary aldosteronism; PAC, plasma aldosterone concentration; ref, reference range; UFC, urinary free cortisol.

Introduction

It has been reported that pregnancy is a state of excess cortisol, even under normal circumstances. Both the blood total cortisol and urinary free cortisol (UFC) levels become approximately 2 to 3 times higher than those in nonpregnant women as pregnancy progresses (1). Therefore, if Cushing syndrome (CS) is present before pregnancy, the pathological condition might be aggravated by pregnancy. However, pregnancy combined with CS is rare. Because untreated CS is often associated with amenorrhea and hypogonadism, CS patients usually have difficulty becoming pregnant. In addition, CS in pregnancy is challenging to identify and diagnose since features of CS can overlap with symptoms of pregnancy (weight gain, insulin resistance, hypertension, etc.); additionally, dynamic testing for CS in pregnancy is challenging due to hormonal changes, such as estrogen-induced cortisol binding globulin synthesis or placental adrenocorticotropic hormone (ACTH) secretion. There are also very few reports of patients becoming pregnant after being diagnosed with CS (2). Therefore, details about how the cortisol level and symptoms change before and during pregnancy are not well known. Furthermore, CS with primary aldosteronism (PA) during pregnancy is very rare (3). There are no reports that describe CS and PA before conception and during pregnancy. We were able to follow the course of a pregnant woman with CS from before pregnancy to after delivery. Although she had adrenal CS and irregular menstruation, she became pregnant naturally prior to receiving treatment. In addition, the patient had coexisting PA, although it was mild. Physical signs and hormonal levels were well controlled by our multidisciplinary treatment during pregnancy. Nevertheless, the delivery was complicated by placental abruption, and the mother presented with compression fractures after delivery. We describe her clinical course and hormonal data throughout the pregnancy.

Case Presentation

A 38-year-old woman was referred to our department for the examination of a right adrenal incidentaloma recognized by abdominal ultrasonography during a physical checkup. She was admitted to our hospital for the hormonal functions of the tumor to be investigated. At age 36, she had undergone surgical resection of a uterine myoma; subsequently, she developed deep venous thrombosis (DVT) and received anti-coagulant therapy for 4 months until the thrombus disappeared. Her past maximum weight at age 37 was 62.6 kg

Table 1. Laboratory findings before and during pregnancy

Reference range	Before pregnancy	At 13 to 14 weeks of pregnancy	At 18 weeks of pregnancy with metyrapone	At 21 weeks of pregnancy after adrenalectomy
Lymphocyte count				
>1000/µL	1571/µL	669/µL	1409/µL	2200/µL
Serum K				
3.6-4.8 mEq/L	3.7 mEq/L	3.1 mEq/L	4.0 mEq/L	3.6 mEq/L
3.6-4.8 mmol/L	3.7 mmol/L	3.1 mmol/L	4.0 mmol/L	3.6 mmol/L
ACTH				
7-63 pg/mL	3 pg/mL	2 pg/mL	1 pg/mL	2 pg/mL
1.54-13.87 pmol/L	0.66 pmol/L	0.44 pmol/L	0.22 pmol/L	0.44 pmol/L
Serum cortisol				
4.0-18.3 µg/dL	14 µg/dL	20.2 µg/dL	17.4 µg/dL	3.3 µg/dL
110.4-504.9 nmol/L	386.3 nmol/L	557.3 nmol/L	480.1 nmol/L	91.0 nmol/L
UFC				
11.2-80.3 µg/day	230.4 µg/day	640 µg/day	164.3 µg/day	507 µg/day[a]
30.9-221.5 nmol/day	635.7 nmol/day	1765.8 nmol/day	453.3 nmol/day	1398.8 nmol/day[a]
PAC				
30.0-159.0 pg/mL	106.4 pg/mL	29.1 pg/mL	30.7 pg/mL	37.7 pg/mL
83.1-440.4 pmol/L	294.7 pmol/L	80.6 pmol/L	85.0 pmol/L	104.4 pmol/L
PRA				
0.2-2.7 ng/mL/h	0.4 ng/mL/h	2.3 ng/mL/h	3.3 ng/mL/h	2.6 ng/mL/h
0.2-2.7 µg/L/h	0.4 µg/L/h	2.3 µg/L/h	3.3 µg/L/h	2.6 µg/L/h

Abbreviations: ACTH, adrenocorticotropic hormone; PAC, plasma aldosterone concentration; PRA, plasma renin activity; UFC, urinary free cortisol.
[a]With hydrocortisone supplementation.

(BMI 23.0 kg/m²). When hospitalized at age 38, her body height was 164.9 cm, and her body weight was 56.9 kg (20.9 kg/m²). Her blood pressure and pulse rate were 126/78 mmHg and 57/minute, respectively, with a regular rhythm. She appeared healthy but had a few areas of submandibular acne and irregular menstruation. Other Cushing phenomena were not observed. She did not have diabetes (HbA1c: 5.8% NGSP [reference range [ref], 4.6%-6.2%]). Her laboratory tests did not indicate hypokalemia or lymphocytopenia, but her UFC level was high (230.4 µg/day [ref, 11.2-80.3 µg/day]; 635.7 nmol/day [ref, 30.9-221.5 nmol/day]) (Table 1). Diurnal variation in blood cortisol disappeared. Morning ACTH level was low (2 pg/mL [ref, 7-63 pg/mL]; 0.44 pmol/L [ref, 1.54-13.87 pmol/L]). A 1 mg dexamethasone suppression test showed an unsuppressed cortisol level (15.6 µg/dL [ref, <1.8 µg/dL]; 430.4 nmol/L [ref, <49.7 nmol/L]). Magnetic resonance imaging (MRI) revealed a right adrenal mass 3.4 cm in size, suggesting adrenal CS (Fig. 1). Although it was not necessary to check her aldosterone-to-renin ratio (4), we checked it according to Japanese practical rules and found that it was elevated (266 pg/mL/ng/mL/h [ref, <200]; 738.2 pmol/L/µg/L/h [ref, <554]). Therefore, she also underwent a captopril challenge test and saline infusion test (Tables 2 and 3). Both tests were positive, and she was assumed to have PA in addition to CS. To identify the source of excess aldosterone and cure CS, we planned to perform adrenal venous sampling for PA and surgical resection of the right adrenal tumor for CS.

Two months after the first admission, however, natural pregnancy (primigravida) was confirmed. She was determined to be at 9 weeks of pregnancy by fetal ultrasonographic examination. At 11 weeks, a 75-g oral glucose tolerance test was performed (Table 4), and she was diagnosed with gestational diabetes mellitus (GDM).

At 14 weeks of pregnancy, she complained of fatigue and lower leg edema, and she had developed "moon face." She was hospitalized again. Her UFC level at 13 weeks was 640 µg/day (1765.8 nmol/day), higher than that before pregnancy. She also presented with a low CD4 count (270/µL: ref, 700-1300/µL) and hypokalemia (3.1 mEq/L [3.6-4.8 mEq/L]; 3.1 mmol/L [3.6-4.8 mmol/L]). MRI and ultrasonography showed no major changes in the size or features of the right adrenal tumor, despite hormonal deterioration (Fig. 1).

On the other hand, her plasma aldosterone concentration (PAC) did not increase during pregnancy. Her blood pressure was also normal, at approximately 105/50 mmHg.

Treatment

Since she had a history of DVT, subcutaneous heparin injection therapy was started to prevent DVT from 12 weeks of pregnancy. GDM was treated with insulin detemir and lispro. She started to take metyrapone 500 mg/day and supplemental potassium beginning at 14 weeks of pregnancy prior to the operation. The dose of metyrapone was gradually increased to 1500 mg/day, without side effects. Laparoscopic right adrenalectomy was performed at 19 weeks of pregnancy, without major complications.

Outcome and Follow-Up

The UFC and plasma cortisol levels decreased with metyrapone, and the lymphocyte counts and serum potassium levels
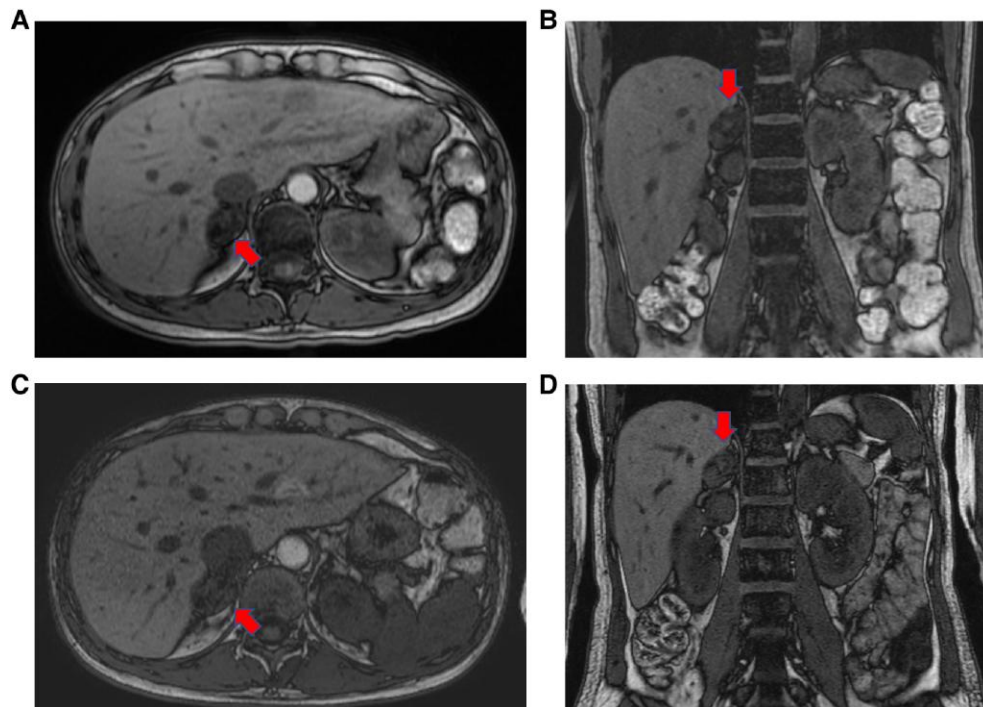
Figure 1. A, B, Adrenal gland on magnetic resonance imaging before pregnancy (T1 weighted, out of phase). Solid arrows indicate the right adrenal mass (34 mm ×24 mm ×22 mm). C, D, Adrenal gland on magnetic resonance imaging at 14 weeks of pregnancy (T1 weighted, out of phase). Solid arrows indicate the right adrenal mass (32 mm ×24 mm ×21 mm). There were no remarkable changes in size or features between examinations.

Table 2. Captopril challenge test

	0 minutes	60 minutes	90 minutes
PAC (pg/mL [pmol/L])	78.1 [217]	78.1 [217]	74.4 [206]
PRA (ng/mL/h [µg/L/h])	<0.2 [<0.2]	<0.2 [<0.2]	0.3 [0.3]

Reference: aldosterone to renin ratio > 200 (pg/mL/ng/mL/h) [>554 (pmol/L/µg/L/h)] at 60 minutes and/or 90 minutes was defined as a positive result.
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.

Table 3. Saline infusion test

	0 hour	4 hour
PAC (pg/mL [pmol/L])	106.4 [295.3]	88.6 [245.9]
PRA (ng/mL/h [µg/L/h])	0.4 [0.4]	0.2 [0.2]

Reference: PAC level > 60 (pg/mL) [>166.2 (pmol/L)] at 4 hours was defined as a positive result.
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.

were normalized before the operation. Her general condition improved at 17 weeks of pregnancy. Metyrapone administration was stopped one day before the surgery.

After the removal of the right adrenal adenoma, her symptoms were ameliorated drastically. The total required amount of insulin decreased by approximately half, and supplementation with potassium was tapered until no longer needed. The hydrocortisone replacement dose was 200 mg on the day of surgery and tapered gradually. Her PAC remained low (40.7 pg/mL [ref, 30.0-159.0 pg/mL, recumbent]; 112.9 pmol/L [ref, 83.1-440.4 pmol/L, recumbent]). The fetus did not have a low weight or intrauterine growth retardation.

Examination of the resected tissue confirmed an adrenocortical adenoma related to CS and diffuse hyperplasia of the zona glomerulosa related to PA (Fig. 2).

The childbirth labor started at 37 weeks and 6 days of pregnancy. Vacuum extraction–assisted delivery was performed due to premature abruption of the placenta. A male infant weighing 2450 g with an Apgar score of 3 at 1 minute was delivered and managed in our neonatal intensive care unit. Corticosteroids were administered to the baby for 3 days and discontinued without adrenal insufficiency. He recovered with no complications and was discharged 24

days after delivery. The infant grew well without any developmental delays thereafter and showed no major congenital anomalies.

The mother was discharged 12 days after delivery. Her insulin therapy was stopped on the day of delivery, and her blood glucose levels were normal afterward. The hydrocortisone replacement dose was 200 mg on the day of delivery and was tapered gradually. However, the mother complained of progressive back pain, and MRI showed thoracic (T8, T9, T10, and T12) and lumbar (L2 and L3) compression fractures. Dual x-ray analysis revealed severe osteoporosis, with a Z-score of −4.8 in the lumbar spine (evaluated at L4, which was not fractured) and −2.1 in the femoral neck. Blood examination showed low 25-hydroxy vitamin D levels (9 ng/mL [ref, >20 ng/mL]; 22.5 nmol/L [ref, >49.9 nmol/L]). Teriparatide and vitamin D therapy was initiated, and breastfeeding was terminated. Regarding PA, her blood pressure and serum potassium level remained stable with no medication.

Discussion

In this case, a woman with CS and PA became pregnant, and her CS deteriorated. She was treated with metyrapone and

underwent adrenalectomy. She remained stable after the treatment; however, premature abruption and compression fractures occurred later. Her PA was mild and had little effect on

Table 4. 75-g oral glucose tolerance test

	0 minutes	60 minutes	120 minutes
Blood glucose (mg/dL [mmol/L])	90 [5.0]	224 [12.4]	148 [8.2]
Reference range	<92 [<5.1]	<180 [<10]	<153 [<8.5]

her pregnancy course. This case is unique because spontaneous pregnancy in CS patients is prevented due to hypercortisolemia. Indeed, this patient became pregnant despite having irregular menstruation.

In normal pregnancy, the serum cortisol and UFC levels become approximately twice as high in the second trimester than in nonpregnancy (1). The action of estrogen increases cortisol binding globulin and prolongs the half-life of blood cortisol; therefore, the total and free cortisol levels increase. There have been only a few reports of pregnancy with CS (2). In the present case, a significant increase in the patient's UFC level was already observed in the first trimester. We also
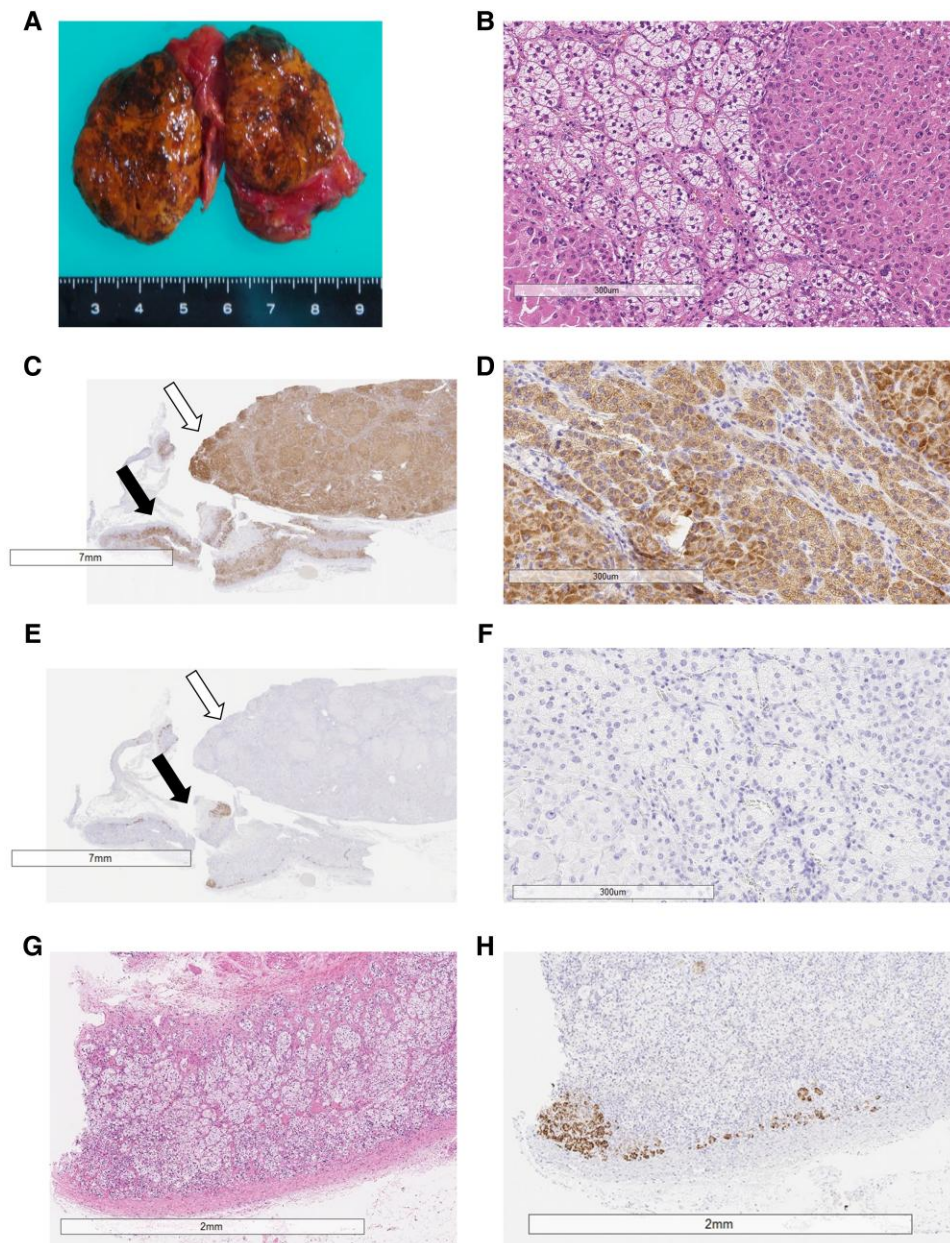

Figure 2. Surgical specimen and histological results. A, Gross pathology. B, Hematoxylin and eosin (HE) staining with strong magnification of the tumor lesion. C, CYP11B1 staining with weak magnification and strong staining of the tumor lesion (open arrow). Staining of accompanying adrenal tissue (solid arrow). D, CYP11B1 staining with strong magnification of the tumor lesion. E, CYP11B2 staining with weak magnification and no staining of the tumor lesion (open arrow). F, CYP11B2 staining with strong magnification of the tumor lesion. G, HE staining with moderate magnification of adrenal tissue, showing diffuse hyperplasia of the zona glomerulosa. H, CYP11B2 staining with moderate magnification of adrenal tissue, showing positive staining of the zona glomerulosa with CYP11B2.

confirmed that the increase in UFC was not due to growth or alteration of the adrenal tumor (Fig. 1). We should assume that the symptoms of CS will become aggravated by pregnancy, even if a patient has few Cushing symptoms before pregnancy, and that such aggravation could occur during the first trimester.

Adrenalectomy is recommended for adrenal CS treatment, even in pregnancy (5). Metyrapone administration can also be considered (5). We selected adrenalectomy for the treatment of CS and succeeded. We decided to administer metyrapone before surgery because of the emerging trend of hypercortisolemia deteriorating lymphocytopenia.

After surgical resection, the patient's symptoms improved drastically. However, premature abruption of the placenta occurred. There are reports that the rates of premature birth and low birth weight among CS mothers cannot be improved even with therapeutic intervention during pregnancy, although the live birth rate can be improved (5). It is possible that hypercortisolemia during the early stage of pregnancy influences the risk of these outcomes. Placental abruption might also be caused by connective tissue weakness due to exposure to large amounts of cortisol during early pregnancy. Careful observation should be performed even when treatment improves CS symptoms. In addition, contraception is necessary for women of childbearing age for whom a complete cure has not been obtained.

For PA during pregnancy, it is uncertain whether hypertension and hypokalemia might resolve due to the anti-mineralocorticoid effect of progesterone (6) or deteriorate because of the increased PAC (7). In this case, the patient had both PA and CS. The pathological examination showed diffuse hyperplasia of the zona glomerulosa, which usually causes idiopathic hyperaldosteronism and a lower PAC than aldosterone-producing adenoma (8, 9). Eventually, CS deteriorated the pregnancy course, while PA did not.

The patient presented with multiple spinal compression fractures after childbirth. Hypercortisolemia is an important factor of osteoporosis. Clinicians should be aware of the importance of assessing bone mineral density as soon as possible after delivery when the mother has CS, even if it has been treated. It is also important to revise the consumption of calcium-rich food products and check vitamin D levels in every patient with CS after hypercortisolism is confirmed.

In conclusion, we were able to follow the full course of pregnancy in a woman with both CS and PA from before pregnancy to after delivery. After conception, symptoms of CS became apparent. Lymphocytopenia, hypokalemia, and GDM were observed and treated. Although medical and surgical treatment was appropriately performed during pregnancy, placental abruption and compression fractures occurred. Clinicians should pay attention to the risks associated with CS even after treatment during pregnancy.

Learning Points

- Cushing syndrome probably worsens during pregnancy.
- There are residual risks if the treatment of Cushing syndrome is successful during pregnancy.
- Primary aldosteronism does not always deteriorate the pregnancy course if Cushing syndrome is also present.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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