

A Case of ACTH-Producing Pheochromocytoma Associated with Pregnancy

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Abstract. Ectopic ACTH syndrome is rarely caused by pheochromocytoma. We report a case of a 28-year-old woman with Cushing's syndrome due to ACTH-producing adrenal pheochromocytoma. She had delivered preterm baby at 32nd week of gestation with 'severe preeclampsia'. After delivery, persistent hypertension accompanied by severe headache led her to being misdiagnosed as Cushing's syndrome due to right adrenal adenoma (normal plasma ACTH level) and cerebral vasculitis of unknown etiology. She was referred to our hospital for surgical treatment. Repeated biochemical studies suggested coexistence of ectopic ACTH syndrome and pheochromocytoma. To reverse her clinical deterioration, right total and left subtotal adrenalectomy was performed with presumptive diagnosis of 1) right adrenal pheochromocytoma causing ectopic ACTH syndrome or 2) coexistence of ACTH-dependent Cushing's syndrome and right adrenal pheochromocytoma. Pathologic examination of right adrenal mass revealed pheochromocytoma which showed strong immunostaining for ACTH. Plasma ACTH and urinary cortisol excretion normalized after surgery, but she succumbed to multiple cerebral infarcts and disseminated intravascular coagulation. Pregnancy and inappropriately low plasma ACTH at initial evaluation might have hampered early diagnosis. To our knowledge, this is the first description of a case with ectopic ACTH syndrome due to pheochromocytoma associated with pregnancy.

Key words: Pheochromocytoma, Cushing's syndrome, Pregnancy, Adrenal

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CUSHING'S syndrome caused by ACTH-producing pheochromocytoma has been rarely reported, ranging from 3 to 25 % of the ectopic ACTH syndrome [1–3]. Most cases of ectopic ACTH syndrome are associated with small cell lung carcinoma, bronchial carcinoid or medullary carcinoma of thyroid. Typical clinical manifestations of Cushing's syndrome may be absent or minimal in cases with ectopic ACTH syndrome due to small cell lung carcinoma. In contrast, those by carcinoid tumors or pheochromocytoma have longer

clinical courses and usually exhibit typical cushingoid features [4, 5].

Early diagnosis of Cushing's syndrome and pheochromocytoma needs high index of suspicion. Symptoms and signs of both diseases may be nonspecific and typical clinical features may be absent in some cases. Furthermore, cyclic or periodic hormone production by tumors and minimally increased levels of hormone and their metabolites, sometimes render the biochemical diagnosis enigmatic. In addition, the physiological increase of hormone levels during pregnancy may mimic both diseases and the misdiagnosis as preeclampsia is not uncommon [6, 7].

We report here a case of Cushing's syndrome due to ACTH-producing pheochromocytoma who initially presented with hypertension and headache during pregnancy.

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Case report

A 28-year-old woman presented with moon face, palpitation and proximal muscle weakness. At 30th week of pregnancy, severe headache developed, and she was diagnosed as pregnancy-induced hypertension. The patient delivered her baby at 32nd week of pregnancy because of preeclampsia. One month after delivery, headache reappeared and the cause of headache was systematically examined at a regional hospital. Magnetic resonance imaging (MRI) of brain showed multiple foci of high signal intensity mainly involving cortex, and cerebral angiography showed multi-focal narrowing of cerebral arteries. These findings led to the diagnosis of cerebral vasculitis, but no definite cause of vasculitis was found. Although headache improved with analgesics, hypertension had been refractory to medications. An evaluation for secondary hypertension was done. Basal serum cortisol levels were 1150 nmol/L (41.7 µg/dL) [normal range (NR) 55–772 nmol/L] and 1404 nmol/L (50.9 µg/dL) at 8:00 AM and 4:00 PM, respectively. Plasma ACTH levels were 5.3 pmol/L (24.2 pg/mL) (NR 2–13 pmol/L) and 7.5 pmol/L (34.2 pg/mL) at 8:00 AM and 4:00 PM, respectively. However, plasma epinephrine [0.93 nmol/L (0.17 ng/mL) (NR < 1.64 nmol/L)] and norepinephrine level [3.05 nmol/L (0.52 ng/mL) (NR < 4.73 nmol/L)] were not elevated. A 24-h urine free cortisol after the standard low dose dexamethasone (DXM) suppression (0.5 mg every 6 h for 48 h) was 3448 nmol/day (1250 µg/day), which led to diagnosis of Cushing's syndrome. Computed tomography (CT) scan of abdomen revealed a hypertrophic change of left adrenal gland and a 3 × 5 cm-sized right adrenal mass which was well defined and not enhanced (Fig. 1). A diagnosis of Cushing's syndrome due to functioning right adrenal cortical adenoma was made, and she was referred to our hospital for resection of the tumor.

She had taken carvedilol (25 mg every 12 h), calcium channel blocker (diltiazem, 90 mg every 12 h) and α-adrenergic blocker (prazosin 2 mg every 12 h) for the control of blood pressure, and had insulin injections (50 units/day) for glycemic control. However, blood pressure was 150/100 mmHg with marked fluctuation (190/110–140/90 mmHg). Physical examination revealed truncal obesity, brown follicular papules on face and trunk, and pitting edema on both lower extremities. She had been bed-ridden for weeks due to

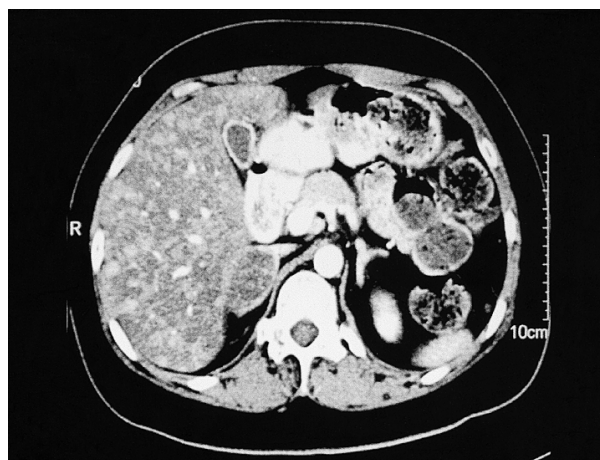


Fig. 1. Computed tomography scan showed 3 × 4 cm sized mass in right adrenal gland and hypertrophied both adrenal glands.

severe proximal muscle weakness. A complete blood count at the time of admission showed a shift to the left with WBC $6.2 \times 10^9/L$ (89% neutrophils/10% lymphocytes/0.2% eosinophils/1% monocytes), and serum electrolyte measurement showed marked hypokalemia (2.6 mmol/L). Fasting serum glucose levels was 8.2 mmol/L (147 mg/dL), and hemoglobin A_{1c} was 8.2%.

The non-suppressed serum ACTH, hypertrophic change of left adrenal gland, intermittent palpitation accompanied by perspiration and hypertension resistant to drug therapy, prompted us to think that the culprit lesion causing Cushing's syndrome might not be a cortisol-producing adrenal adenoma. Thus, endocrine tests for both ACTH-dependent Cushing's syndrome and pheochromocytoma were conducted. The baseline serum cortisol levels were 3145 nmol/L (114 µg/dL) (NR 55–689 nmol/L) and 2483 nmol/L (90 µg/dL) (NR 80–330 nmol/L) at 8:00 AM and 4:00 PM, respectively (Table 1). Plasma ACTH level measured at our hospital was 144.2 pmol/L (655 pg/mL) (NR 1–13 pmol/L). A 24-h urine free cortisol was 5482 nmol/day (1987 µg/day) (NR 55–248 nmol/day). Both low and high dose DXM suppression test (0.5 mg and 2 mg every 6 h for 48 h, respectively) showed that 24-h urine free cortisol excretion increased to 7901 nmol/day (2864 µg/day) and to 9198 nmol/day (3334 µg/day), respectively. Extremely elevated plasma ACTH levels and non-suppressed 24-h urine free cortisol by the administration of high dose DXM, suggested that the cause of endogenous hypercortisolemia was ec-

Table 1. Hormonal studies before and after operation

| Hormonal Profiles | (Reference Range) | Before operation | After operation |
|------------------------------|--------------------------|------------------|-----------------|
| Serum cortisol concentration | | | |
| 8:00 A.M. | (55–689 nmol/L) | 3145 | 714 |
| 4:00 P.M. | (80–330 nmol/L) | 2483 | – |
| Serum ACTH concentration | (1–13 pmol/L) | 144.2 | 5.7 |
| 24-hour urine free cortisol | (55–248 nmol/day) | 5482 | 126 |
| After low-dose suppression | | 7901 | – |
| After high-dose suppression | | 9198 | – |
| 24h urine VMA | (3.5–34.8 μ mol/day) | 222.0 | – |
| 24h urine metanephrine | (<6.5 μ mol/day) | 13.7 | – |
| 24h urine epinephrine | (< 275 nmol/day) | 1649 | |
| 24h urine norepinephrine | (89–473 nmol/day) | 4257 | |

topic ACTH syndrome. A 24-h urine collection study revealed a markedly elevated excretion of vanillylmandelic acid (VMA) [222.0 μ mol/day (44.0 mg/day) (NR 3.5–34.8 μ mol/day)], metanephrine [13.7 μ mol/day (2.5 mg/day) (NR < 6.5 μ mol/day)], epinephrine [1649 nmol/day (302 μ g/day) (NR < 275 nmol/day)], and norepinephrine [4257 nmol/day (720 μ g/day) (NR 89–473 nmol/day)].

Brain MRI done at the previous hospital demonstrated no evidence of pituitary adenoma. Chest CT showed no pulmonary or mediastinal mass. 123 I meta-iodobenzylguanidine (MIBG) scan revealed no focus of increased uptake in 4-hour image, and delayed image could not be obtained due to drowsy mental change.

Based on radiologic and biochemical studies, two presumptive diagnoses were made; the first was the coexistence of ACTH-dependent Cushing's syndrome and right adrenal pheochromocytoma, and the second was an ACTH-producing right adrenal pheochromocytoma. We decided to postpone inferior petrosal sinus and adrenal vein sampling with CRH stimulation because of the risk of paroxysm. Adrenal MRI was not performed. Prazosin (5 mg every 8 h) and propranolol (20 mg every 8 h) was required for the control of blood pressure.

On 10th hospital day, she became stuporous, but there was no definite focal neurologic deficit. Brain CT revealed several new low-density lesions in deep white matter, however those could not explain mental change. Cerebrospinal tapping was performed and analysis of CSF supported bacterial meningitis. Clinical condition deteriorated in spite of intensive therapy including broad-spectrum antibiotics. As the only possible way to reverse her clinical deterioration was to

reduce hypercortisolism and since cortisol-lowering therapy with ketoconazole could not be used because of her poor hepatic function, right total and left subtotal adrenalectomy was performed under intravenous replacement of hydrocortisone at a dose of 50 mg every 8 h. Pathologic examination revealed a medullary pheochromocytoma of right adrenal gland with strongly positive ACTH staining and cortical hyperplasia of both adrenal glands. The levels of serum cortisol, plasma ACTH and 24-h urine free cortisol excretion were 714 nmol/L (25.9 μ g/dL), 5.7 pmol/L (20.7 pg/mL) and 126 nmol/L (45.6 μ g/day) on the 3rd postoperative day, respectively (Table 1).

In spite of successful removal of pheochromocytoma which was the source of ectopic ACTH secretion, her mental status further deteriorated. Brain CT scan was repeatedly performed, and it showed extensive cerebral infarct accompanied by cerebral edema, suggesting the existence of septic emboli. No microorganism was detected in blood and CSF cultures. Dexamethasone (4.0 mg every 6 h) and mannitol was administered in order to reduce cerebral edema, and empirical antibiotics, including vancomycin (1.0 g every 12 h), ceftriaxone (2.0 g every 12 h) and ampicillin (2.0 g every 4 h) was started. However, her mental status was not improved and she developed sepsis immediately followed by refractory disseminated intravascular coagulation. Despite aggressive therapy with antibiotics and vasopressor, she expired with a picture of multiple organ failure 2 weeks after the adrenalectomy. Request for an autopsy was not granted.

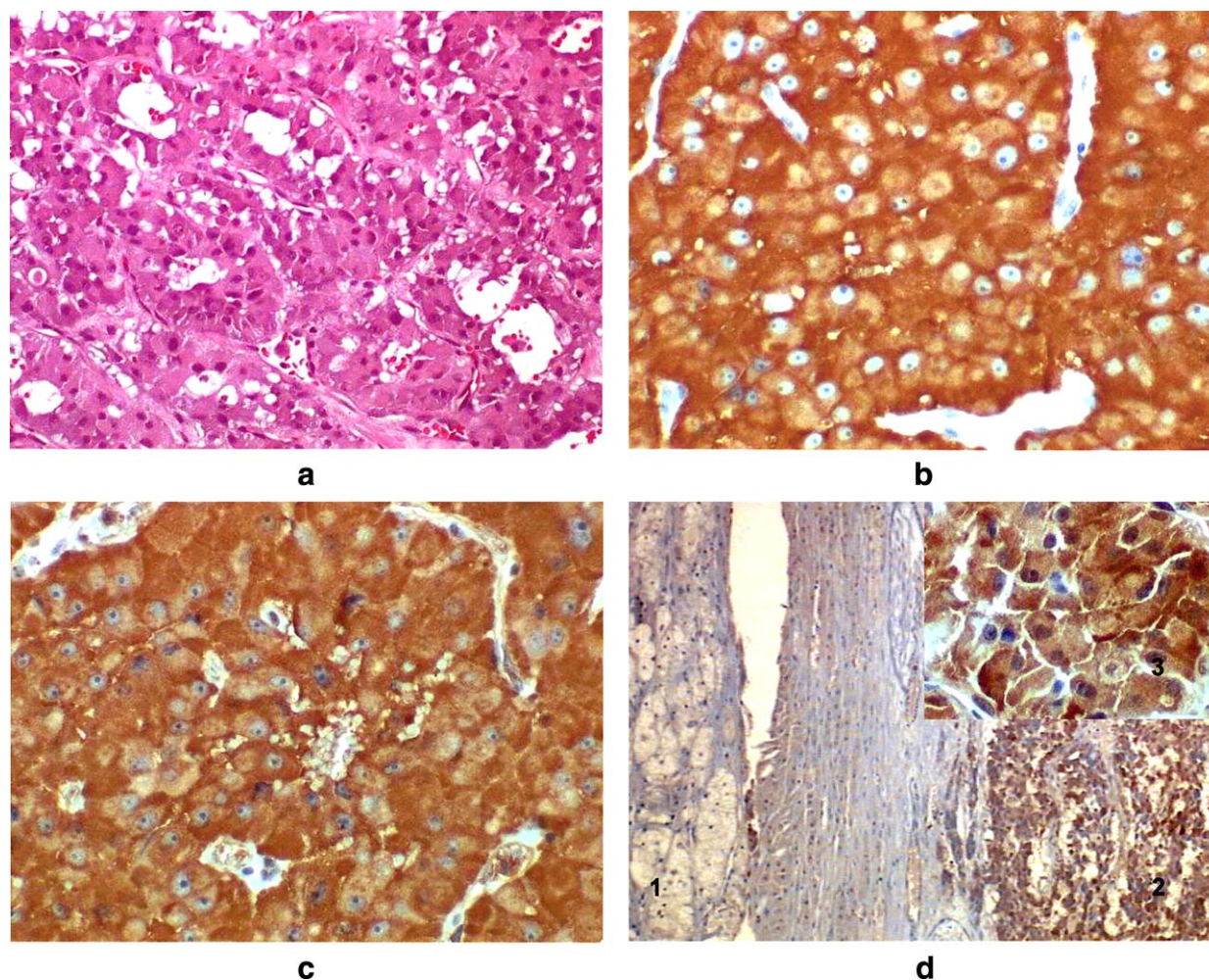


Fig. 2. Histology and immunohistochemistry of tumor showed typical findings of pheochromocytoma (a, H&E, $\times 200$) and positivity for synaptophysin (b, $\times 200$), chromogranin (c, $\times 200$) and ACTH (d, $\times 40$). 1, hyperplastic tissue; 2, adenoma; 3, high power view of adenoma ($\times 200$).

Histology and immunohistochemistry

Right adrenal gland measured $7.5 \times 3.5 \times 2.5$ cm and weighed 40 gm. It consisted of hypertrophic gland and $4 \times 4 \times 3$ cm-sized tumor. The excised left adrenal gland measured $7.5 \times 3.5 \times 1.5$ cm, and weighed 18 gm. Hemorrhagic fluid gushed out from a cut section of right adrenal tumor, and the cut surface was yellowish-to-white solid with multicystic degeneration. Microscopic examination of the right adrenal mass showed oval to polygonal cells with abundant cytoplasmic granule and with increased vascularity, being consistent with pheochromocytoma (Fig. 2a). Both adrenal glands showed cortical hyperplasia.

The immunohistochemistry of right adrenal tumor

showed positivity for synaptophysin (Monoclonal Mouse Anti-synaptophysin, Clone SY 38, DAKO Corp.) and chromogranin (Monoclonal Mouse Anti-human chromogranin A, Clone DAK-A3, DAKO Corp.), confirming pheochromocytoma (Fig. 2b, 2c). The tumor cells showed strongly positive staining for ACTH (Polyclonal Anti-Human ACTH, A0571, DAKO Corp.) (Fig. 2d).

Discussion

Diagnosis of Cushing's syndrome might have been delayed possibly due to the confounding effect of pregnancy in this case. Corticotropin releasing

hormone (CRH) is produced by placenta, decidua, and fetal membranes from 8th – 10th week of gestation, and the plasma CRH binding protein level falls in late pregnancy. The increase in CRH induces ACTH secretion and consequently relative hypercortisolism occurs even in normal pregnancy [8]. Thus, it is sometimes difficult to diagnose Cushing's syndrome in late pregnancy. Moreover, both hypertension and classical symptoms of pheochromocytoma, such as headache, palpitation, and sweating, occur less frequently in pregnant patients [6], rendering suspicion of pheochromocytoma difficult.

Excessive ACTH and/or glucocorticoid inhibit GnRH and therefore induce infertility. Considering the fact that the pregnancy in this case was possible and maintained without any fetal problem until early third trimester, we can postulate the cortisolemic effect might have been minimal at the time of conception. To the best of our knowledge, only one case with pheochromocytoma and subclinical Cushing's syndrome during pregnancy has ever been reported [9]. However, the tumor was negative for ACTH immunostaining, and thus the increased level of interleukin-6 produced by the tumor was suggested as the mechanism of increased cortisol production in that case. In our case, the adrenal adenoma was strongly positive for the immunostaining and although demonstration of POMC mRNA expression was omitted, it was confirmed that the tumor was an ACTH-secreting tumor. It is unique that the adrenal pheochromocytoma was proved to have been the source of ectopic ACTH syndrome based on pathologic confirmation after surgery.

Although a rare case of intermittent hypercortisolism in ectopic ACTH syndrome was reported [10], the pulsatility of plasma ACTH level is known to be virtually absent in patients with ectopic ACTH syndrome [11]. Therefore, the discrepancy of ACTH levels between the first test (5.3 pmol/L) and the second one in our hospital (144.2 pmol/L) may be explained as a laboratory error or as a different method of quantitation, considering that the ACTH precursor, but not ACTH itself, usually correlates with the plasma cortisol levels in ectopic ACTH-producing syndrome [11, 12]. In addition, plasma ACTH level

was detectable (5.7 pmol/L) even after successful adrenalectomy in this case. It has been reported that continuous infusion of CRH can stimulate plasma ACTH secretion after successful treatment of Cushing's disease although the response was blunted [13], and that severe stress induces the release of CRH. This means that the suppressed plasma ACTH level in treated patients with Cushing's syndrome is not only due to suppressed function of pituitary corticotrophs, but due to depressed CRH secretion. Thus, the non-suppressed plasma ACTH level after adrenal surgery could have been caused by severe stressful condition in this case.

This patient initially presented with severe headache, which improved after delivery but finally led her to medical evaluation. Her previous neurologist made a diagnosis of cerebral vasculitis of unknown etiology after the detection of multifocal arterial narrowing and cerebral cortical infarct on brain MRI and cerebral angiography. In retrospective view, her cerebral vasculitis might have been the result of catecholamine excess caused by pheochromocytoma. Excess catecholamine from pheochromocytoma is known to induce vasospasm resembling vasculitis, which is reversible after correction of underlying disease. This reversible catecholamine-mediated vasospasm has been designated as "pseudovasculitis" [14]. In this patient, combined infection and illness might have aggravated catecholamine excess and consequent cerebral ischemia due to vasospasm leading to new cerebral infarcts, which was found in immediate postoperative period.

In this case, adrenal pheochromocytoma proved to be the source of ectopic ACTH syndrome based on repeated biochemical studies and pathologic confirmation after surgery. In spite of successful removal of pheochromocytoma and resolution of endogenous hypercortisolism, full-blown sepsis followed by refractory disseminated intravascular coagulation led to patient death. To our knowledge, this is the first description of a case with ectopic ACTH syndrome caused by pheochromocytoma associated with pregnancy.

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