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DIFFICULT CASE

Case of Adrenocorticotropic Hormone–Independent Macronodular Adrenal Hyperplasia with Possible Adrenal Hypersensitivity to Angiotensin II

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With increasing case reports, it has been indicated that some cases with adrenocorticotropic hormone (ACTH)–independent macronodular adrenal hyperplasia (AIMAH) show abnormal responses in cortisol to various stimulation tests. Here we report a case of AIMAH that showed an aberrant response to angiotensin II via AT1 receptor in cortisol hypersecretion. A 53-yr-old man was admitted to our division seeking further examinations for the possible diagnosis of Cushing's syndrome. He had hypertension, diabetes mellitus, and physical stigmata, such as moon face and central obesity. His plasma ACTH level was undetectable, and plasma cortisol level was high. Plasma cortisol showed no normal diurnal rhythm and was not suppressed after the administration of 8 mg of dexamethasone. Abdominal computed tomography demonstrated nodular enlargement of bilateral adrenal glands. He was diagnosed with Cushing's syndrome owing to AIMAH. An injection of arginine vasopressin (AVP) increased plasma cortisol and aldosterone levels, whereas ACTH remained undetectable. After 4 h in an upright position, plasma cortisol and aldosterone levels were increased. Pretreatment with candesartan, angiotensin II receptor AT1 antagonist, blocked the increase in plasma cortisol level. These results suggested a possibility of adrenal hypersensitivity to angiotensin II and AVP in cortisol secretion. Bilateral laparoscopic adrenalectomy was performed. The histological findings of the specimen were compatible with AIMAH. In summary, we have made the first report on a case of AIMAH with possible hypersensitivity to angiotensin II.

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Introduction

Cushing's syndrome is caused by two types of pathogenesis: adrenocorticotropic hormone (ACTH)–dependent (in ACTH-producing pituitary adenoma and ectopic ACTH-producing tumors) and ACTH-independent (in adrenocortical adenoma and carcinoma) *(1)*. ACTH-independent macronodular adrenal hyperplasia (AIMAH) has recently been recognized as a distinct subtype of ACTH-independent Cushing's syndrome *(2,3)*. With increasing case reports, it has been indicated that some cases with AIMAH show abnormal responses in cortisol to various stimulation tests, such as tests with arginine vasopressin (AVP) *(4–9)*, cathecholamine *(9)*, luteinizing hormone (LH) *(10)*, serotonin 5HT4 receptor agonists *(10)*, gastric inhibitory polypeptide (GIP) *(11,12)*, and leptin *(13)*. Although bilateral macronodular adrenal hyperplasia was formerly thought to result from a long-standing ACTH hypersecretion from a pituitary tumor *(14,15)*, some investigators have recently proposed a possible involvement of aberrant receptor expression, which may be responsible for such abnormal responses, in the pathogenesis of AIMAH *(4)*. Here we report a case of AIMAH that suggested an aberrant response to angiotensin II via AT1 receptor in cortisol hypersecretion and discuss the relation of the adrenal hypersensitivity to the pathophysiology of AIMAH.

Case Report

A 53-yr-old man was admitted to a hospital complaining of abdominal distension. He was diagnosed with possible Cushing's syndrome. He was admitted to our division for further examinations. He had hypertension, diabetes mellitus, and physical stigmata typical of Cushing's syndrome, such as moon face, central obesity, and muscle weakness.

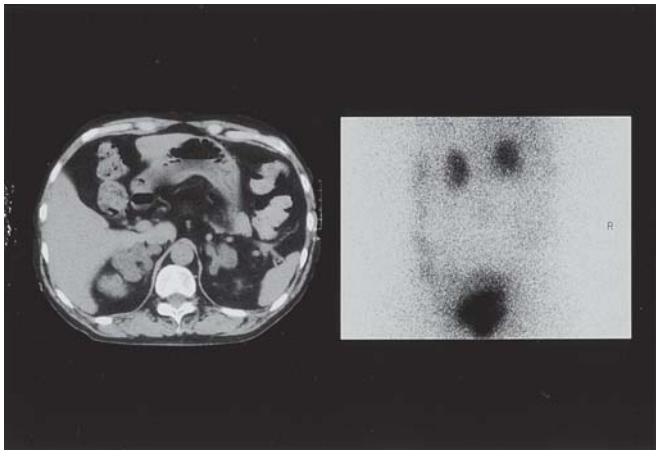


Fig. 1. (Left) Abdominal CT of the patient demonstrating nodular enlargement of bilateral adrenal glands; **(right)** iodocholesterol scintigraphy while taking 2 mg of dexamethasone daily, which reveals a marked uptake of radioactivity into the bilateral adrenal glands.

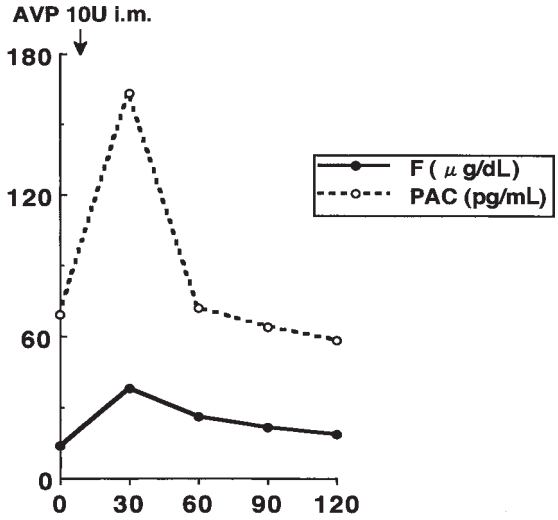


Fig. 2. AVP loading test (10 U intramuscularly). F, plasma cortisol concentration (μg/dL); PAC, plasma aldosterone concentration (pg/mL).

He had taken 80 mg of furosemide daily for 3 yr, which was administered by a nearby physician. On evaluation of adrenocortical function, while the plasma ACTH level was undetectable (<4.0 pg/mL), the plasma cortisol level was high (22.1 μg/dL). Plasma cortisol showed no normal diurnal rhythm and was not suppressed (21.1 μg/dL) after the administration of 8 mg dexamethasone. Abdominal computed tomography (CT) demonstrated nodular enlargement of bilateral adrenal glands (Fig. 1, left), and iodocholesterol scintigraphy while taking 2 mg of dexamethasone daily revealed a strong uptake into the bilateral adrenal glands (Fig. 1, right). No abnormalities were observed in the pituitary on magnetic resonance imaging of the brain.

On endocrinologic loading tests, synthetic 1-24 ACTH administration (0.25 mg intravenously) evoked plasma cortisol and aldosterone secretion (17 to 53.8 μg/dL and 50.7 to 105 pg/mL, respectively). An im injection of 10 U of AVP increased plasma cortisol and aldosterone levels, whereas the plasma ACTH level remained undetectable (Fig. 2). After the patient remained in an upright position for 4 h followed by 30 min in a supine position for the baseline plasma cortisol and aldosterone measurements, plasma cortisol and aldosterone levels were increased (Fig. 3, left). Pretreatment with candesartan (8 mg) blocked the increase in plasma cortisol level (Fig. 3, right). For the 5% hypertonic saline infusion test (0.05 mL/[kg·min] for 2 h), the plasma cortisol level was unchanged and the plasma aldosterone level was suppressed, while the plasma AVP level showed a normal increase responding to the elevation of serum osmolarity (Table 1). No response of ACTH, cortisol, and aldosterone was observed for corticotropin-releasing hormone, thyrotropin-releasing hormone, growth hormone–releasing hormone (GRH), luteinizing hormone–releasing hormone, meal, and a 5HT4 agonist, mosapride (10 mg, orally) (data not shown).

These results indicated a diagnosis of Cushing's syndrome due to AIMAH with adrenal hypersensitivity to angiotensin II and AVP in cortisol secretion. Bilateral laparoscopic adrenalectomy was performed, which revealed bilateral adrenal tumors (100 g, 75 × 37 × 31 mm on the right, and 90 g, 78 × 32 × 27 mm on the left). On microscopic examination, the adrenal tumor specimens were composed of clear cortical cells and small compact cells (Fig. 4A). Normal portion of adenocortical tissue was not detected. Immunohistochemical examination of steroidogenic enzymes revealed immunoreactivity of all enzymes including P450scc, 3β-HSD, P450c21, P450c11, P450c17, and dehydroepiandrosterone sulfotransferase. 3β-HSD immunoreactivity was detected only in clear cortical cells (Fig. 4B), and P450c17 immunoreactivity only in compact cells (Fig. 4C). These histological findings were compatible with AIMAH *(16)*.

Discussion

AIMAH is a distinct subtype of Cushing's syndrome, of which the exact pathogenetic mechanism remains unclear. Recently, it has been reported that some agents, such as AVP, GIP, catecholamine, LH, 5HT4 agonists, and leptin, aberrantly evoked cortisol secretion in AIMAH *(4,13)*. These abnormal responses are considered to be partly due to overexpression of eutopic receptors in the adrenal such as V1-AVP and GIP receptors *(4)*. Although AVP can stimulate cortisol secretion in vitro only at a pharmacologic dose *(17)*, GIP cannot, even in vitro *(11)*. Functional β-adrenergic receptors are not expressed in normal human adrenal cortex *(9)*. A case of AIMAH with abnormal adrenal response to AVP was reported in which a gross overexpression of V1-AVP receptor was not demonstrated *(7)*. Moreover, leptin, which has a physiologic inhibitory role in cortisol secretion

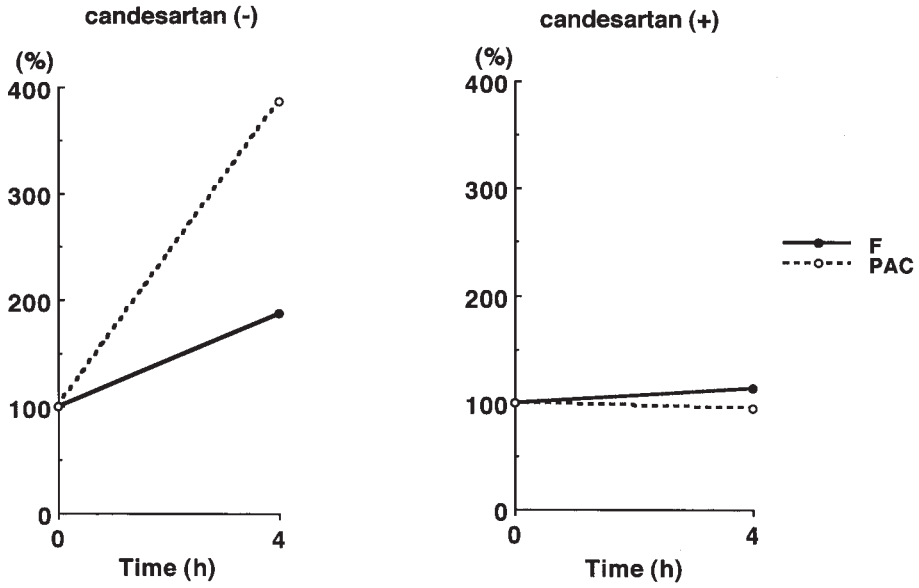
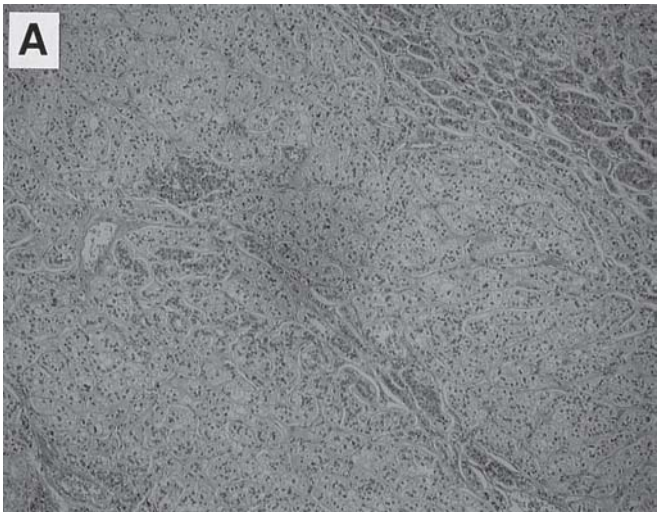
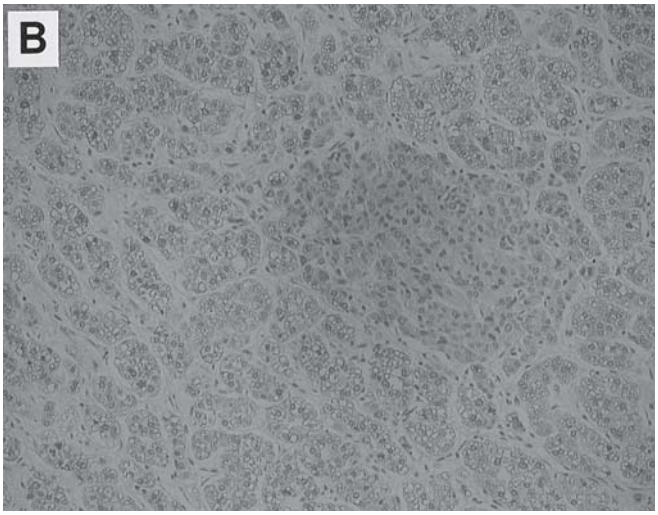


Fig. 3. Upright posture (4 h) test. Changes in plasma cortisol and aldosterone levels without **(left)** or with **(right)** pretreatment with 8 mg of candesartan are demonstrated. Each hormone concentration after upright posture is shown as a percentage of baseline value. F, plasma cortisol concentration; PAC, plasma aldosterone concentration.

Table 1
5% Hyperton Saline Infusion Text

		5% Hypertonic saline infusion	
		Before	After
Serum osmolarity	(mOsm/kg)	287	305
Plasma AVP	(pg/mL)	1.1	6.7
Plasma cortisol	(μg/dL)	17.3	16.7
Plasma aldosterone	(pg/mL)	44.2	<25.0





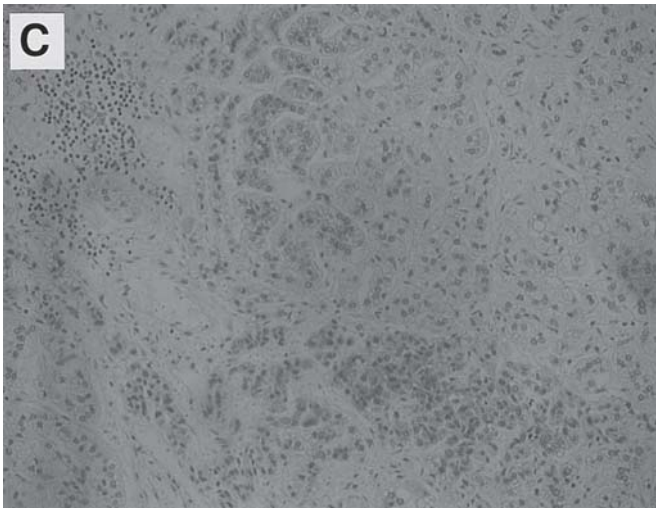


Fig. 4. Microscopic examination of the resected adrenal tumor specimen. **(A)** Hematoxylin and eosin stain. The nodules were composed of clear cortical cells and compact cells. **(B,C)** Immunohistochemical examination of steroidogenic enzymes. 3β-HSD **(B)** was expressed only in clear cortical cells, and P450c17 **(C)** only in compact cells.

(18), caused cortisol hypersecretion in a case of food-dependent Cushing's syndrome *(13)*. These findings suggest a possibility that somatic mutations of genes involving receptor-effector systems or regulating receptor expression in the adrenal cortex might be involved in, although such mutations have not been detected yet, and we did not examine the clonality of macronodular adrenals in the present study.

In our case, the upright position stimulated cortisol secretion about two times, as reported by Lacroix et al. *(9)*, in which the β-adrenergic antagonist propranolol blocked the increase and reduced urinary cortisol secretion. The upright posture evokes an increase in plasma renin activity by stimulating sympathetic systems, leading to elevation of plasma angiotensin II concentration *(19)*. It is well known that angiotensin II stimulates aldosterone secretion mainly through angiotensin II receptor, AT1 *(20)*. However, there has been no evidence, to our knowledge, that angiotensin II affects cortisol secretion in vivo. Angiotensin II stimulated cortisol secretion only slightly, but not to a significant degree, in human adrenal primary culture derived from normal subjects *(21)* and in patients with Cushing's syndrome *(22)*. In our case, pretreatment of candesartan, an AT1 antagonist, blocked the increase in plasma cortisol level. On the other hand, neither the angiotensin-converting enzyme inhibitor captopril *(9)* nor the AT1 antagonist losartan *(23)* blocked this increase in plasma cortisol concentration induced by the posture test in the other case *(9,23)*. These findings suggested that angiotensin II aberrantly stimulated cortisol secretion via AT1 receptor, although the angiotensin II loading test and in vitro examination were not performed. AVP also evoked cortisol secretion as well as angiotensin II in our case. We performed 5% hypertonic saline loading test for the purpose of determining which of the two mechanisms might be involved in hypercortisolism in our case: hypersensitivity to angiotensin II or that to AVP. Hypertonic saline infusion, which stimulates endogenous AVP secretion *(24)* and suppresses the renin-angiotensin system *(19)*, did not increase plasma cortisol level, indicating that hypercortisolism in this case might be caused by hypersensitivity of AT1 receptor rather than by that of AVP-V1 receptor. It is reported that angiotensin II stimulates adrenocortical cell growth *(25)*. Therefore, it is possible that the adrenal hypersensitivity to angiotensin II is involved in the pathogenesis of AIMAH in cases such as the present one. Moreover, our case patient had taken furosemide for 3 yr, which might have stimulated angiotensin II and AVP secretion, leading to the progression of AIMAH.

Trials with several pharmacological agents have been reported in some cases of AIMAH *(4)*. Octreotide *(12)* and V1a receptor antagonist *(7)* were used for short term in GIP- and AVP-dependent AIMAH, respectively. Long-term control of cortisol secretion was achieved with propranolol *(9)* and leuprolide acetate *(10)* in cases with abnormal responses to catecholamine and LH, respectively. In the present case, bilateral adrenalectomy was performed, but it seems possible that medical therapy with AT1 blocker may ameliorate hypercortisolism in cases in which angiotensin II hypersensitivity can be documented.

In summary, we have reported a case of AIMAH with hypersensitivity to angiotensin II. Considering the effect of angiotensin II in adrenal cell growth, it is plausible that the hypersensitivity is involved in the pathogenesis of AIMAH. Further investigations are required if long-term treatment with AT1 receptor antagonist is to have an effect on the size of adrenal enlargement or the hypercortisolism, which clarify the significance of abnormal adrenal response to angiotensin II.

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