

# Adrenocorticotropin-Independent Bilateral Adrenal Macronodular Hyperplasia (AIMAH) : A Case Report

Min-Huang Hsieh<sup>1</sup>, Ching-Chung Chang, Min-Chieh Lin<sup>2</sup>, and Tien-Chun Chang

*Division of Endocrinology and Metabolism, Department of Internal Medicine,  
National Taiwan University Hospital, Taipei, Taiwan*

<sup>2</sup>*Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan*

<sup>1</sup>*Division of Endocrinology and Metabolism, Department of Internal Medicine,  
China Medical University Hospital, Taichung, Taiwan*

## Abstract

**Background** : ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing's syndrome (CS), which is characterized by massive bilateral nodular enlargement of adrenal glands and hypercortisolism in the presence of suppressed ACTH levels. **Case** : A 53 year-old woman with a 5-year history of hypertension was referred to our hospital for further evaluation of bilateral adrenal tumors with macronodules, which were detected by computed tomography. She presented with a weight gain of 3 kg over the previous 6 months and pitting edema. Endocrinological data of the patient showed ACTH-independent hypercortisolemia. CS due to AIMAH was suspected. She underwent simultaneous bilateral laparoscopic adrenalectomy. The histopathological analysis confirmed the diagnosis. She was on cortisone acetate (37.5mg per day) replacement therapy postoperatively. No hyperpigmentation was present and she was being well. Her weight declined gradually and her blood pressure was controlled better with less doses of antihypertensive agents during follow-up. **Conclusion** : AIMAH is an unusual type of Cushing's syndrome. Bilateral adrenalectomy with subsequent steroid replacement is the treatment of choice in patients with AIMAH and CS. ( J Intern Med Taiwan 2006; 17: 291-297 )

**Key Words** : ACTH-independent macronodular adrenal hyperplasia (AIMAH), Cushing's syndrome (CS), Laparoscopic adrenalectomy

## Text

ACTH-independent macronodular adrenal hyperplasia (AIMAH) is an unusual cause of Cushing's syndrome (CS), which is characterized by massive bilateral nodular enlargement of adrenal glands and hypercortisolism in the presence of suppressed ACTH levels<sup>1,2</sup>. The diagnosis is usually based on clinical manifestations, and bilateral adrenal nodular enlargement on imaging studies following the demonstration of hypersecretion of cortisol and suppressed plasma ACTH level. The final diagnosis is established by pathologic examination<sup>3</sup>. Bilateral adrenalectomy with subsequent steroid replacement is considered to be a standard therapy for AIMAH. Here we present a case of AIMAH in a 53 year-old woman who underwent bilateral laparoscopic adrenalectomy.

## Case report

A 53 year-old Taiwanese woman had been diagnosed with hypertension at the age of 48 and treated with calcium channel blockers and  $\beta$ -adrenergic antagonist since then. Although she took antihypertensive agents regularly, her blood pressure was not controlled well. She was a housewife, had a past history of bilateral nephrolithiasis and neither smoking nor alcohol consumption. Her mother had hypertension also. She presented with muscle weakness, palpitations, pitting edema of the legs and weight gain of 3 kg over the previous 6 months. Bilateral adrenal macronodular masses were detected by renal sonography and subsequent computed tomography (CT) scan, measuring 6 cm in maximal diameter in the right adrenal gland and 3.5 cm in maximal diameter in the left (Figure 1A and 1B). She was referred to our hospital for further evaluation.

At admission, her height was 165 cm and she weighted 70 kg, with body mass index (BMI) 25.7 kg/m<sup>2</sup>. Her pulse rate was 60 beats per minute and blood pressure was 147/94 mmHg. Physical exami-

nations revealed a typical cushingoid appearance: moon face, plethora, buffalo hump, central obesity and pretibial edema. There were no hyperpigmentation, violaceous striae, ecchymosis or skin thinning. The thyroid gland was non-palpable.

Routine laboratory examinations showed hypokalemia ( $K^+$ : 3.1 mmol/L, with reference range 3.5 ~ 5.3 mmol/L) and hypercholesterolemia (total cholesterol: 226 mg/dL, with reference range less than 220 mg/dL). The fasting plasma glucose level was 78 mg/dL and the serum triglyceride level was 129 mg/dL.

The results of the endocrinological examinations were summarized in Table 1. The circadian variation of serum cortisol production was absent and the basal level of ACTH was suppressed. There was no

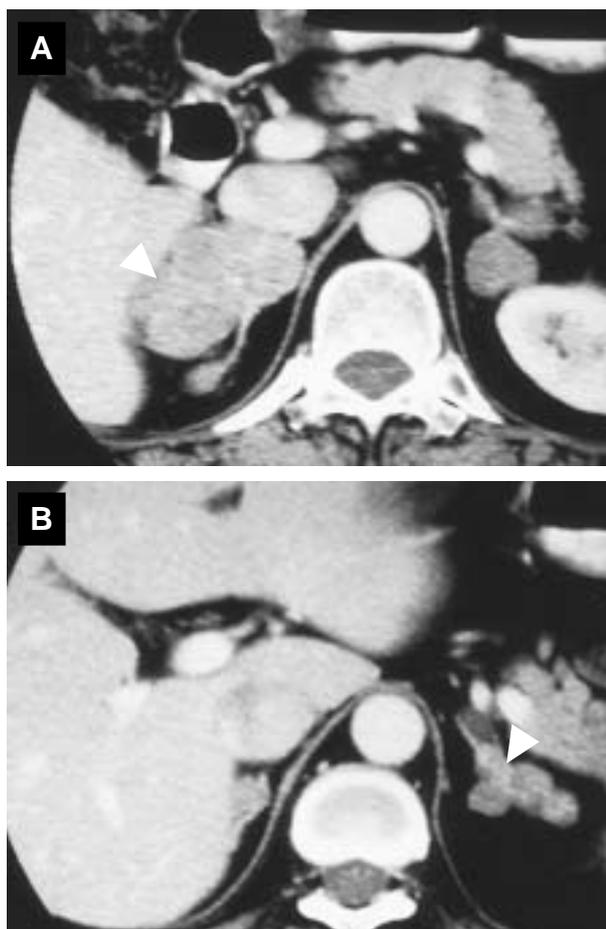


Fig.1. Computed tomography with contrast media of the adrenal gland showed nodular enlargement of right (A) and left (B) adrenal glands (arrows).

suppression of serum cortisol with an overnight dexamethasone suppression test. Magnetic resonance imaging (MRI) of sella turcica revealed no pituitary tumor. After investigation, laparoscopic removal of bilateral adrenal tumors was performed. The pathological examination showed that both adrenals were diffusely enlarged with multinodules; the right adrenal gland was 9.5 x 7.5 x 3.3 cm in size and weighted 110 g (Figure 2A) and the left adrenal gland was 7.6 x 7.0 x 2.8 cm in size and weighted 48 g, with multiple golden yellow nodules measuring 2.5 cm in diameter. Microscopically, these nodules were composed predominantly of hyperplastic clear cells, accompanied by internodular hyperplasia. (Figure

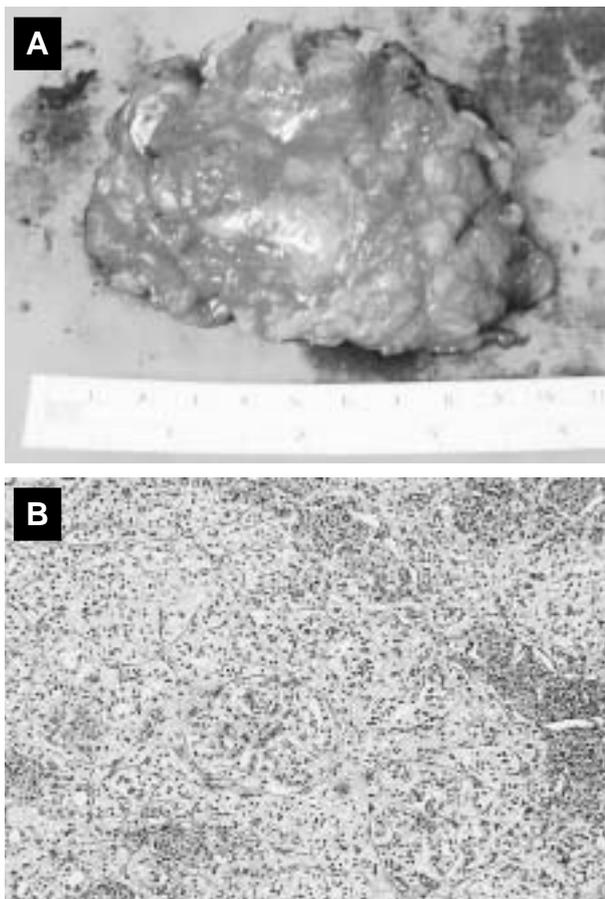


Fig.2. Grossly, multiple yellowish nodules were present in the resected right adrenal gland, which was 9.5 x 7.5 x 3.3 cm in size (A). Microscopically, the adrenal tissue was composed predominantly of clear cells, demonstrating adrenocortical hyperplasia (B) (Hematoxylin-eosin staining, original magnification x 40).

2B). The final clinical and pathological diagnosis was Cushing's syndrome secondary to AIMAH.

We followed this case for 7 months. Cortisone acetate 37.5 mg was given daily for replacement postoperatively. She lost weight gradually. Her blood pressure was controlled better with less doses of antihypertensive agents. Besides, she was being well subjectively without hyperpigmentation.

## Discussion

In the adult population, primary adrenal hypersecretion accounts for approximately 15-20% of all endogenous Cushing's syndrome<sup>1</sup>. Unilateral adrenocortical adenomas and rarely, carcinomas, represent the majority of adrenal pathologies causing CS. Compared with the previous literatures, however, an obviously higher percentage of adrenal causes of CS has been reported in Taiwan<sup>4</sup>.

Bilateral adrenal pathology developing excess cortisol secretion represents approximately 10-15% of all adrenal causes of CS and includes: primary pigmented nodular adrenocortical disease (PPNAD), which is usually associated with Carney's complex; AIMAH, and bilateral adrenal adenomas or carcinomas<sup>1</sup>. AIMAH is thus a very unusual cause of CS of endogenous etiology.

AIMAH was first described by Kirshner et al in 1964<sup>5</sup>. A greater number of cases have been reported in the literatures since then. Although the clinical presentation of AIMAH is usually hypercortisolism with CS, concurrent secretion of glucocorticoid and mineralcorticoid, or glucocorticoid and sex steroid (estrone) has been reported. Occasionally, predominant enlargement of the unilateral adrenal gland is found in cases with AIMAH. Subclinical CS has been described to occur in patients with AIMAH in recent years<sup>6</sup>.

The presentation of AIMAH has a bimodal distribution. Some may develop in the first year of life with McCune-Albright syndrome<sup>7</sup>, whereas most patients present in the 5th decade of life. Unlike the pre-

dominant female distribution in most endogenous CS, the female: male ratio is almost 1:1 in cases with AIMAH<sup>3</sup>. Male predominance has been reported in some series.

In the majority of cases, AIMAH presents as a sporadic disorder. Family AIMAH has rarely been reported, because familial screening is lacking in most cases and some subclinical form might have not been identified. The presentation of familial AIMAH suggests autosomal-dominant transmission and implies some mutation involving steroidogenesis in the affected adrenal nodules<sup>8</sup>. The definite genetic background is not understood currently. A few cases of AIMAH have been reported in the literatures to be associated with McCune-Albright syndrome (gain-of-function mutation of *GNAS1* gene), familial adenomatous polyposis (mutation of *APC* gene) and multiple endocrine neoplasia syndrome type 1 (mutation of *MENIN* gene)<sup>6</sup>. Further gene microarray analysis of sporadic cases and the familial clustering may help us to clarify the pathogenesis of AIMAH on the molecular pathway.

The diagnosis of AIMAH is usually based on clinical manifestations of CS, and bilateral adrenal nodular enlargement on imaging studies following the demonstration of hypercortisolism and unde-

tectable plasma ACTH level. The final diagnosis is established by histopathologic examination of the adrenal tissue. Pathologically, the weight of bilateral adrenals in AIMAH is usually greater than 60 g, in comparison with that in patients with ACTH-dependent Cushing's disease. Histologically, AIMAH is composed of two cell types, those with a clear cytoplasm (lipid-rich) that form cordon nest-like structures and those with a compact cytoplasm (lipid-poor) that form nests or island-like structures<sup>9</sup>. Internodular atrophy or hyperplasia has been described. Despite greater adrenal enlargement, laboratory examination may reveal only mild elevation of cortisol level, suggesting ineffective cortisol production by individual adrenal cells and greater cell numbers required to develop cortisol excess and clinical manifestations<sup>10</sup>. Some deficiency in enzymes responsible for steroidogenesis in the adrenal cortex had been documented<sup>6</sup>.

The pathogenesis of AIMAH remains unknown. ACTH had been thought to be a stimulatory factor to promote adrenal nodular growth and steroidogenesis, in which the resultant adrenal autonomy eventually suppressed ACTH production<sup>11,12</sup>. Nelson's syndrome, however, developed rarely following bilateral adrenalectomy in these patients, arguing against

Table 1. Endocrinological data

		Patient's value	Reference range
Plasma ACTH ( pg/mL )	8AM	< 5.00	10 ~ 65
	4PM	< 5.00	10 ~ 65
Serum cortisol ( $\mu$ g/dL )	8AM	25.8	5 ~ 25
	4PM	18.7	2.5 ~ 12.5
	8AM, after dexamethasone 1mg at 11PM	19.0	
DHEA-S ( $\mu$ mol/L )		< 0.8	4.6 ~ 15.4
VMA (mg/24h)	24h-urine	3.7	1 ~ 7
Dopamine ( $\mu$ g/24h )	24h-urine	141.6	50 ~ 450
Epinephrine ( $\mu$ g/24h )	24h-urine	< 4.2	< 22.4
Norepinephrine ( $\mu$ g/24h )	24h-urine	19.6	12.1 ~ 85.5
iPTH ( pg/mL )		74.1	12 ~ 72
HbA1c (%)		5.7	3.8 ~ 6.0

VMA: vanillylmandelic acid, DHEA-S: dehydroepiandrosterone sulfate, iPTH: intact parathyroid hormone, HbA1c: hemoglobin A1c

this hypothesis. Measurement of basal and postadrenalectomy plasma ACTH may be helpful to elucidate whether ACTH plays a causal role. On the other hand, the interpretation of postoperative ACTH value may be complicated by suppression of hypothalamus-pituitary axis by prolonged hypercortisolism and subsequent steroid replacement. Furthermore, since the measurement of plasma ACTH or serum cortisol levels seems impractical to determine the optimal dose of steroid replacement, we did not obtain the postoperative ACTH value in this case. We propose that a long-standing stimulation other than ACTH through some receptor or some alteration in the post-receptor downstream signaling pathway in the adrenal gland may be implicated in the pathogenesis of nodular adrenocortical hyperplasia and cortisol hypersecretion. Recently, a novel pathogenetic mechanism of AIMAH has been mentioned. Several groups have demonstrated that *in vivo* the hypersecretion of cortisol is mediated by some hormones other than ACTH. To date, ectopic or aberrant adrenal expression of various membrane hormone and/or cytokine receptors coupled to G-protein to promote steroidogenesis, such as catecholamines, vasopressin, gastric inhibitory polypeptide (GIP), angiotensin, serotonin, luteinizing hormone/human chorionic gonadotropin (LH/hCG), leptin and prostaglandin E1, have been identified, and corticosterone production is responsive to these ligands/agonists *in vitro*<sup>6,13</sup>. By blocking the aberrant receptors and suppressing the endogenous ligands, it provides us some novel pharmacological therapies to treat selected patients with AIMAH and CS. In this case we described, however, no investigative test to characterize these aberrant receptors was performed.

Bilateral adrenalectomy with steroid replacement is the treatment of choice. Although the adrenal mass in AIMAH is usually larger than other types of adrenal tumors, with skilled and experienced surgeons, laparoscopic surgery is also feasible in those patients<sup>14</sup>. Unilateral adrenalectomy has been advo-

cated and it may be suitable in patients with predominantly enlarged unilateral adrenal gland, thus avoiding lifetime steroid replacement. Close follow-up of the residual gland and monitoring of metabolic syndrome are necessary. Medical treatment with mitotane, metyrapone and ketoconazole has been reported in selective subjects with AIMAH and CS.

In conclusion, AIMAH is a very rare etiology of Cushing's syndrome we have encountered. The definite pathogenic mechanism is not understood well. Adrenalectomy with steroid replacement is the current mainstay treatment, whereas some novel medical therapies through antagonizing the ectopic or aberrant receptors of the adrenal cortex to inhibit steroidogenesis may have a role in the future.

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# 非促腎上腺皮質激素依賴型大結節性腎上腺皮質過度增生：病例報告

謝旻晃<sup>1</sup> 張慶忠 林明杰<sup>2</sup> 張天鈞

國立台灣大學醫學院附設醫院內科部代謝內分泌科

<sup>2</sup> 國立台灣大學醫學院附設醫院病理科

<sup>1</sup> 中國醫藥大學附設醫院內科部代謝內分泌科

## 摘 要

非促腎上腺皮質激素依賴型大結節性腎上腺皮質過度增生是造成庫欣氏症候群一個很罕見的原因。它的特色是臨床上有庫欣氏症候群的表現，生化檢查會發現高皮質醇血症和低促腎上腺皮質激素，影像學上常可見兩側腎上腺結節性腫大。診斷的標準還是要靠病理組織檢查。我們在此報告一位患有高血壓的53歲女性病人被診斷為非促腎上腺皮質激素依賴型大結節性腎上腺皮質過度增生。接受經內視鏡兩側腎上腺切除和類固醇補充治療後，病人自覺整體狀況良好，而且她的血壓變得比較好控制，體重也逐漸下降。目前她還在門診持續追蹤治療中。