Intraadrenal Adrenocorticotropin Production in Bilateral Macronodular Adrenal Hyperplasia: A Case Report and Review of the Literature

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Abstract

ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing's syndrome, which is characterized by massive bilateral nodular enlargement of adrenal glands and hypercortisolism in the presence of suppressed ACTH levels. We reported a 68 year-old woman having a more than 20-year history of hypertension was referred to our hospital for further evaluation of bilateral adrenal macronodular masses. Dynamic endocrinological test showed ACTH–independent hypercortisolemia. AIMAH was suspected. She underwent simultaneous bilateral laparoscopic adrenalectomy. The histopathological analysis confirmed the diagnosis and immunohistochemical studies showed positive ACTH immunoreactivity in a subpopulation of steroidogenic cells, but not in chromaffin cells of the hyperplastic tissue. She was on cortisol acetate replacement therapy postoperatively. No hyperpigmentation was present. Her blood pressure was controlled well with one kind of antihypertensive agent during follow-up. Furthermore, her ACTH level still remained stable postoperatively during follow-up. AIMAH is an unusual type of Cushing's syndrome. Bilateral adrenalectomy with subsequent steroid replacement is the treatment of choice. The intra-adrenal cortex overproduction of ACTH was the probably cause in our case of AIMAH.

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Key words: Cushing's syndrome, ACTH-independent macronodular adrenal hyperplasia, intraadrenal adrenocorticotropin production, bilateral adrenalectomy.

Introduction

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 level. The diagnosis is usually based on
clinical and biochemical hypercortisolism, bilateral adrenal nodular enlargement and suppressed plasma ACTH level. The final diagnosis is established by pathologic proof. Bilateral adrenalectomy with subsequent steroid replacement has been considered to be a standard therapy for AIMAH in the past. Here we presented a case of AIMAH in a woman who underwent bilateral laparoscopic adrenalectomy.

Case report

A 68 year-old Taiwanese woman has been diagnosed with hypertension for more than 20 years and noticed of uncontrolled blood pressure with three kinds of anti-hypertensive drugs. The recent anti-hypertensive regimen included calcium channel blocker, \(\alpha\)-adrenergic antagonist and diuretic. She had osteoporosis history with compression fracture of lumbar spine and had received operation several times during the recent three years. She ever received the exam of bone mineral density, which suggested generalized osteoporosis. She presented with muscle weakness and poor appetite for a 3-month interval. Intermittent upper abdominal pain also complained and duodenal ulcer was noted from upper gastrointestinal panendoscopy. Laboratory analysis showed microcytic anemia, severe hypokalemia (1.9 mmol/L; reference range 3.6-5.2), and metabolic alkalosis. Brain computed tomography (CT) scan was arranged due to severe vertigo and headache, and showed negative finding. Bilateral adrenal macronodular masses were detected by abdominal CT (Figure 1) due to abdominal pain. Bone scan, which was arranged due to bone pain, demonstrated multiple increased activities over multiple ribs, T7, T9, T2, L1 and L2, but left pubic bone mass status post excisional biopsy and revealed no malignancy or granuloma can be found. PET-FDG (Positron Emission Tomography Fluoro-2-deoxy-D-glucose) showed no evidence of focal increased glucose metabolism to suggest malignant disease, but adrenal adenoma may have normal uptake of FDG. The results of the endocrinological evaluation showed the circadian variation of serum cortisol production was absent (am: 23.8 \(\mu\)g/dL, reference range 4.3-22.4; pm: 36.6 \(\mu\)g/dL, reference range 3.1-16.7, respectively) and the basal level of ACTH (<5.0 pg/mL; reference range <46.0) was suppressed. According to the result of 24 hours urine free cortisol (877.8 \(\mu\)g/day; reference range 55.5-286.0), CS was diagnosed. She was referred to our hospital for further evaluation and oral ketoconazole 200mg three times daily was prescribed.

At admission, her height was 148 cm and weighted 46 kg, with body mass index (BMI) of 21.0 kg/m2. Her pulse rate was 80 beats per minute and blood pressure 150/90 mmHg. Physical examination revealed a typical cushingoid appearance of moon face, buffalo hump, central obesity, ecchymosis over limbs, skin thinning, and mild pitting edema. There were no hyperpigmentation or violaceous striae. There was no suppression of serum cortisol with both low-dose and high-dose dexamethasone suppression test (cortisol: 16.5 \(\mu\)g/dL, after dexamethasone 0.5 mg po q6h X 8 doses; cortisol: 11.8 \(\mu\)g/dL, after dexamethasone 2.0 mg po q6h X 8 doses). After investigation, laparoscopic removal of bilateral adrenal masses was performed. Grossly, both adrenal glands were diffusely enlarged with multi-nodularities. The right adrenal gland was 8 x 4 x 2 cm, 71 gm, and 8 x 6 x 2 cm with multiple golden yellow nodules in left adrenal gland (Figure 2). Microscop-
cally, these nodules were predominantly composed of compact proliferative cells with eosinophilic cytoplasm, slightly pleomorphic nuclei, and arranged in a fascicular pattern. Focal clear cell change is also evidently seen (Figure 3a). Diffuse cortical hyperplasia was confirmed. Immunohistochemical studies of hyperplastic tissue showed that ACTH immunoreactivity was detectable in a subpopulation of steroidogenic cells, but not in chromaffin cells (Figure 3b). The immunohistochemical result compared with normal adrenal tissue explants (control tissues), which were obtained from two patients undergoing expanded nephrectomy for kidney cancer, was different. The normal adrenal tissue explants shows no ACTH-positive immunoreactivity in most cortical cell (Figure 3c). The final diagnosis was bilateral macronodular adrenal hyperplasia due to intra-adrenal adrenocorticotropic production according to biochemical and pathological findings. 

The patient discharged and took oral cortisone acetate 37.5 mg daily for replacement postoperatively. During OPD follow-up about six months, no skin hyperpigmentation was present. Her blood pressure was controlled better with one BP-lowering agent. Furthermore, her plasma ACTH levels still remain stable (range: 20.8-45.5 pg/mL) postoperatively.
Discussion

The causes of CS with bilateral nodular adrenocortical diseases include three rare types.\(^1\) The first is ACTH-dependent bilateral macronodular hyperplasia secondary to long-term adrenal stimulation in patients with Cushing's disease or ectopic ACTH syndrome, and the ACTH level usually revealed high or normal. The second one is ACTH-independent primary pigmented micronodular adrenal hyperplasia and Carney complex, in which the adrenal nodules are usually 2 to 4 mm in diameter and the color is black or brown on cut section. The third one is AIMAH, just as in our case, whose basal ACTH level is suppressed and the adrenal nodules are non-pigmented and greater than 5mm in diameter.

AIMAH is an infrequent cause of CS and first described by Kirshner et al in 1964.\(^2\) Most cases of AIMAH present in the fifth and sixth decades. The average age of the patients with AIMAH is 48 years, and the female: male ratio is almost 1:1 in an early study.\(^3\) Most cases of AIMAH came from Japan, and approximately 110 cases had been reported to 2004.\(^4\) AIMAH presents as a sporadic disorder in the majority of cases, but family AIMAH had been reported in siblings.\(^5\)

AIMAH can present as incidental radiological finding or with subclinical\(^6\) or overt CS, occasionally with concurrent secretion of mineralocorticoids\(^7\) or sex steroids.\(^8\) The clinical diagnosis of AIMAH is usually according to clinical manifestations of CS, bilateral adrenal nodular enlargement on imaging studies, and the demonstration of hypercortisolism with suppressed plasma ACTH level.\(^9\) The asymmetrical size appearance of adrenal macronodules in AIMAH has been described,\(^10\) but iodine-131-6-beta-iodomethyl -19-norcholesterol (NP-59) scintigraphy typically shows bilateral uptake.\(^11\)

Generally, each normal adult adrenal gland is approximately 4g in weight.\(^1\) Pathologically, in patients with ACTH-dependent Cushing's disease, the combined adrenal weight was 22.9 g averagely.\(^12\) Relatively, the combined weight of bilateral adrenal glands in AIMAH is usually greater than 60 g\(^6\) and the mean combined weight was 132 g in one study.\(^13\) Histologically, AIMAH is composed of two cell types, one with a clear cytoplasm (lipid-rich) and another with a compact cytoplasm (lipid-poor).\(^14\)

The pathogenesis of AIMAH is heterogeneous. To date, three possible mechanisms have been identified, included aberrant hormone receptors,\(^6,15\) genetic mutations and intra-adrenocortical ACTH production.\(^16\) Now, the most cases of AIMAH arise from aberrant adrenal expression of one or several G-protein-coupled receptors (ectopic receptors or increased activity of eutopic receptors), which can lead to cell proliferation and abnormal regulation of steroidogenesis. The aberrant hormone receptors, which included catecholamines, vasopressin, gastric inhibitory polypeptide, angiotensin, serotonin, luteinizing hormone / human chorionic gonadotropin, thyrotropin, leptin and prostaglandin E1, had been identified. These diagnoses can be made by the dynamic cortisol change in response to stimulus.\(^6,15,16\) The genetic mutations include activating mutations in GNAS1 gene (Gs alpha-subunit mutations),\(^17\) mutation of MENIN gene (multiple endocrine neoplasia syndrome type 1), activating mutations in MC2R gene, mutation of APC gene (familial adenomatous polyposis),\(^6\) high expression of WISP2 gene and SGNE1 gene in GIP-dependent AIMAH,\(^18\) mutation of FH gene (Hereditary leiomyomatosis and renal cell cancer),\(^19\) and mutation of PDE11A gene.\(^20\) The definite genetic background is not understood currently.

Intra-adrenocortical ACTH production is the rare mechanism of AIMAH, and first described in 2003.\(^16\) Herve et al described the presence of ACTH in the hyperplastic adrenal cortex due to ectopic expression of the POMC gene itself and result in ACTH local biosynthesis. The intra-adrenal cortex overproduction of ACTH was the probably cause of AIMAH, because immunohistochemical localization of ACTH was observed in the adrenocortical hyperplastic tissue, as the findings in our case. The clinical data presented hypercortisolism with suppressed plasma ACTH level were owing to the ACTH was rapidly and actively metabolized in situ after binding to its receptor on adrenocortical cells, and had been indicated by Herve et al.\(^16\) Although plasma ACTH
concentration remains the major diagnostic test for differentiating pituitary from adrenal causes of CS, the term of ACTH-independent used to allocate primary adrenal CS may be inappropriate in some cases with hypercorticism and undetectable plasma ACTH levels.

The treatments of AIMAH include pharmacological therapy and surgery. The identification of aberrant receptors can offer a specific pharmacological approach to prevent progression and control abnormal steroidogenesis, such as octreotide, propranolol, and so on.6,8,15 If the pathogenesis is confined to genetic mutations or intra-adrenocortical ACTH production, the treatment of blockade of aberrant receptors may be failed. In this situation, the choice can be made with mitotane, metyrapone, etomidate and ketoconazole, which can use in patients who had no aberrant receptors and can not tolerate surgery or to control cortisol secretion before surgery.21 Bilateral adrenalectomy with lifelong steroid replacement has been the treatment of choice for AIMAH. To avoid lifelong steroid replacement therapy and poor quality of life, unilateral adrenalectomy of the larger adrenal gland had been advocated, and resulted in clinical and laboratory recovery either transient or long-term period.22,23 The residual adrenal gland is needed to be followed up closely and monitoring of metabolic complications of CS are necessary after unilateral adrenalectomy, because sometimes, a second adrenalectomy may become necessary. For accurate selection of patients for unilateral adrenalectomy, maybe assessable the glands size in addition to NP-59 scintigraphy and selective adrenal venous sampling for cortisol level is a better chance of success.22-24

However, several limitations of our case existed. First, we did not perform the investigative test to characterize the aberrant receptors. Second, the test of ACTH stimulation (250 μg, iv) to confirm the characteristic of ACTH-dependent was not done, either.16

In conclusion, AIMAH is an unusual type of CS. The pathogenesis of AIMAH is heterogeneous, and the intra-adrenal cortex overproduction of ACTH was one probably cause of AIMAH, as in our case. Bilateral adrenalectomy with lifelong steroid replacement is the treatment of choice for AIMAH nowadays. Antagonizing the aberrant receptors of the adrenal cortex to inhibit steroidogenesis may have a major role on selected cases of AIMAH in the further.

References


