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CASE REPORT

Improvement of hypercortisolism by β-blocker therapy in subclinical Cushing's syndrome associated with ACTH-independent macronodular adrenocortical hyperplasia

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Abstract A 61-year-old man with hypertension and diabetes was referred for the evaluation of multiple bilateral adrenal tumors. While Cushingoid features were not apparent, an elevated cortisol level in response to a low-dose dexamethasone suppression test (187.7 nmol/l), an elevated urinary cortisol level (170.9 nmol/day), and a weak response to a cosyntropin-releasing hormone (CRH) provocation test were observed. Furthermore, the serum cortisol level increased in response to a posture test or isoproterenol infusion. Accordingly, the patient was diagnosed as having ACTH-independent macronodular adrenal hyperplasia (AIMAH) with subclinical Cushing's syndrome associated with the aberrant expression of β-adrenergic receptors. After 2 months of propranolol therapy, the serum cortisol responses to a posture test and isoproterenol infusion, the cortisol level in response to a low-dose dexamethasone suppression test (102.1 nmol/l), and the urinary cortisol level (165.9 nmol/day) all normalized. While the suppression of cortisol secretion was sustained for 24 months, glucose metabolism and adrenal size were unaffected. To our knowledge, this is the first report of AIMAH accompanied by subclinical Cushing's syndrome associated with the aberrant expression of β-adrenergic receptors. Furthermore, propranolol inhibited cortisol hypersecretion in the present case. Additional cases or controlled studies are needed to determine the potential effect of propranolol on metabolic disorders and adrenal size in patients with AIMAH.

Keywords Subclinical Cushing's syndrome · AIMAH · Catecholamine · β-Blockade

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Introduction

ACTH-independent macronodular adrenal hyperplasia (AIMAH) is an extremely rare disorder characterized by ACTH-independent cortisol oversecretion from bilateral adrenal cortices. The aberrant expressions of receptors for a variety of hormones, including catecholamines, gastric inhibitory polypeptide, vasopressin (AVP), luteinizing hormone (LH), and serotonin, have been shown to mediate cortical secretion in both in vivo and in vitro studies [1–7], resulting in clinically manifest or subclinical Cushing's syndrome.

The cortisol response to the upright posture test is a clinically useful method for determining aberrant catecholamine and/or AVP receptor expression [1–3, 6]. The isoproterenol infusion test and/or the hypertonic saline infusion test can be further used to discriminate between the aberrant expression of catecholamine and AVP receptors [1–3, 6]. In addition, the aberrant expressions of receptors for gastric inhibitory polypeptide, LH, and serotonin can be confirmed by administering a mixed meal, gonadotrophin-releasing hormone (GnRH), and metochroplamide, respectively, [4–7].

While overt Cushing's syndrome is associated with metabolic and cardiovascular abnormalities, the prevalence of these complications in subclinical Cushing's syndrome is unknown [8]. Therefore, whether metabolic disorders in patients with subclinical Cushing's syndrome should be

treated using resection or pharmacologic blockade remains uncertain. In cases of AIMAH accompanied by subclinical Cushing's syndrome in which ectopic receptor expression has been clinically detected, the suppression of possible endogenous ligands of the abnormal receptors or the administration of specific antagonists might be effective for preventing or treating metabolic complications.

Here, we report a patient with AIMAH associated with subclinical Cushing's syndrome in whom cortisol secretion was stimulated by endogenous and exogenous catecholamines. The patient was treated using a β-blocker, and the endocrinological findings and metabolic complications were reassessed after 24 months of treatment.

Case report

A 61-year-old man was referred for the evaluation of multiple bilateral adrenal tumors. His past medical history included a diagnosis of hypertension and diabetes 1 year previously, and he was taking nateglinide (270 mg daily) at the time of his referral. No known family history of endocrine diseases or malignant tumors was present. On physical examination, he was 170 cm tall and weighed 75.0 kg. His pulse was 80 beats-per-minute, and his blood pressure was 148/80 mmHg. Cushingoid features, such as a moon face, buffalo hump, and striae, were not evident. No heart murmurs or crackles were audible.

Abdominal computed tomography (CT) revealed bilateral multiple macronodular adrenal tumors (Fig. 1a). In- and out-of-phase chemical shift magnetic resonance images demonstrated a significant loss-of-signal in the out-of-phase images of bilateral adrenal tumors (data not shown). Iodine-131 adosterol scintigraphy demonstrated a specific uptake in the adrenal regions corresponding to bilateral adrenocortical tumors (data not shown). Laboratory examinations, including a complete blood count, electrolyte serum levels, and renal and liver tests, revealed no abnormalities. The glycosylated hemoglobin and fasting plasma glucose levels were 7.6% and 134 mg/dl, respectively.

Endocrinological evaluation and hormonal assays

Subclinical Cushing's syndrome was diagnosed by the diagnostic criteria of the Research Committee of the Japanese Ministry of Health, Labor and Welfare for adrenal disease [9]. In brief, the criteria includes as the essential conditions (1) a lack of characteristic features for Cushing's syndrome, (2) normal basal serum cortisol levels, and (3) serum cortisol levels higher than 82.8 nmol/l after 1 mg dexamethasone. The diagnosis was defined based on the presence of all these essential conditions and at least one of the following additional criteria: (1) suppression of plasma ACTH (basal plasma ACTH levels less than 2.2 pmol/l and/or decreased response of ACTH after CRH stimulation test), (2) loss of cortisol diurnal rhythm, (3) decreased serum dehydroepiandrosterone-sulfate (DHEA-S) levels.

Plasma ACTH was measured by a two-site immunoradiometric assay (IRMA; Mitsubishi Chemical, Japan). Serum cortisol was determined by ECLusys 2010 cortisol assay (ECL; Roche Diagnostics Co., Germany).

Endocrinological testing revealed an insufficient reduction in the cortisol levels in response to low-dose (1 mg) and high-dose (8 mg) dexamethasone suppression tests (187.7 nmol/l and 121.4 nmol/l, respectively) and a high urinary cortisol level (471.7 nmol/day), despite normal basal cortisol and DHEA-S level (496.8 nmol/l and 0.71 μmol/l, respectively). The ACTH response to 100 μg of cosyntropin-releasing hormone (CRH) was blunted (Fig. 2). Together with radiological findings, this patient was diagnosed as having subclinical Cushing's syndrome, and AIMAH was suspected.

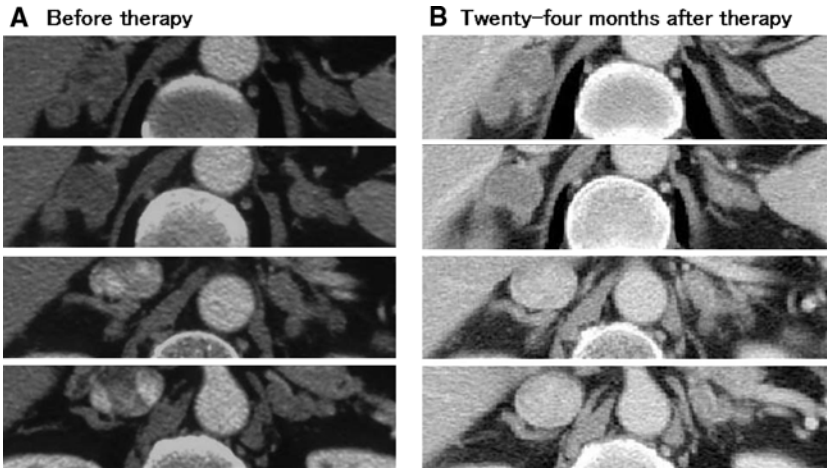

Fig. 1 Computed tomography with contrast injection. **a** Before therapy, multiple macronodular adrenal tumors are visible in bilateral adrenal glands. **b** Twenty-four months after the start of propranolol treatment

Clinical investigation of ectopic receptor expression

After the patient had fasted overnight, a catheter was inserted before 07:30 to avoid stress-related activation of the hypopituitary-adrenal axis in response to venipuncture. The patient rested in a supine position for at least 30 min before the start of testing, which was initiated at 08:00. The investigations were performed sequentially over the course of several days. The screening protocol for ectopic adrenal receptor expression included serial measurements of serum cortisol, ACTH and other hormone levels at defined intervals. Measurements were made after a posture test, after the administration of a standard mixed meal, 100 μg of GnRH, 500 μg of TRH or 10 mg of metoclopramide, and after the administration of isoproterenol (20 ng/kg/min over 30 min) or NaCl (5% at 0.05 ml/kg/min over 120 min). The ethical committee of our institution approved all the protocols, and the patient provided his written informed consent.

An increase in the serum cortisol level from 314.6 to 411.2 nmol/l was observed during the upright posture test (Fig. 3a), and a marked increase in the serum cortisol level from 284.3 to 568.6 nmol/l was observed after isoproterenol infusion (Fig. 3b). The serum cortisol level did not increase after the administration of GnRH (LH increased from 5.4 to 40.6 IU/l), metoclopramide, hypertonic saline infusion (AVP increased from 0.28 to 2.04 pmol/l), or a mixed meal (data not shown).

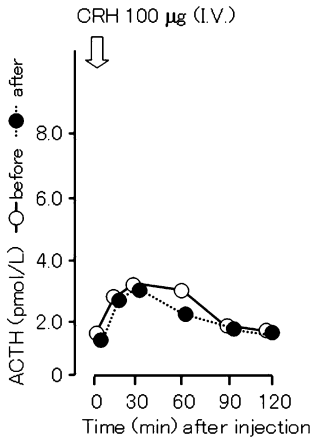

Fig. 2 Intravenous CRH stimulation test (100 μg). The ACTH responses were blunted both before (*open circles*) and after treatment (*closed circles*)

Clinical course after propranolol therapy

Since the aberrant expression of catecholamine receptors was suspected in this patient, treatment with oral propranolol (a long-acting β-blocker) at a daily dose of 60 mg was initiated (Fig. 4). One month after the start of treatment, the dose of propranolol was increased to 120 mg daily (Fig. 4). One month later, the patient was re-admitted for a second endocrinological evaluation. While the responses to the low-dose and high-dose dexamethasone suppression tests (cortisol levels of 102.1 and 85.6 nmol/l, respectively), the urinary cortisol level (165.9 nmol/day), and the blood pressure (Fig. 4) showed evidence of improvement, no change in the ACTH response to 100 μg of CRH was detected (Fig. 2). The serum cortisol response to the upright posture test and to isoproterenol infusion had normalized (Fig. 3a, b).

As the glycosylated hemoglobin level had not improved, a biguanide was added 12 months after the initiation of propranolol therapy (Fig. 4). No changes in the sizes of the bilateral multiple macronodular adrenal tumors were noted on abdominal CT images obtained 24 months after the start of propranolol treatment (Fig. 1a, b).

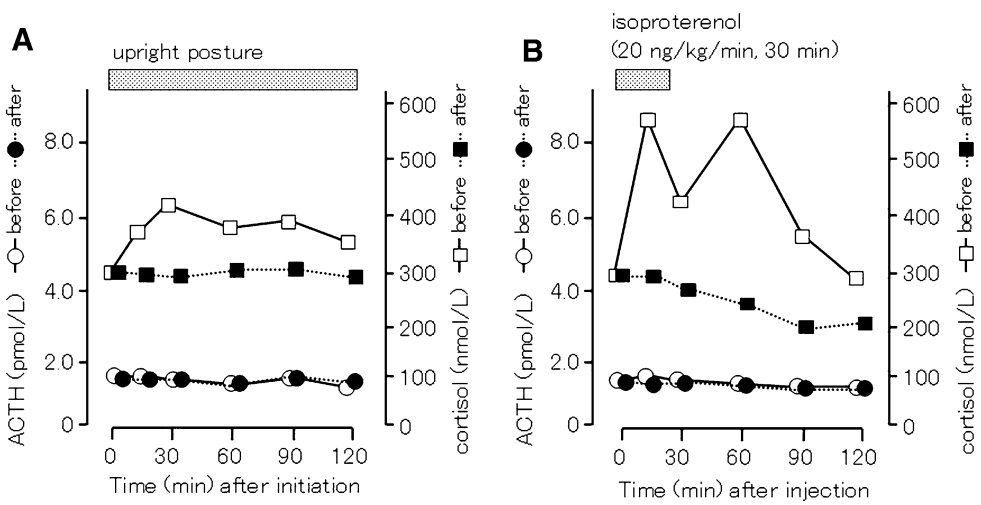

Fig. 3 Serum cortisol responses during screening for aberrant membrane hormone receptors. **a** Upright posture test. **b** Catecholamine infusion test. Serum levels of ACTH and cortisol before propranolol treatment are indicated by the *open circles* and *open squares*, respectively. Serum ACTH and cortisol levels after propranolol treatment are shown by the *closed circles* and *closed squares*, respectively

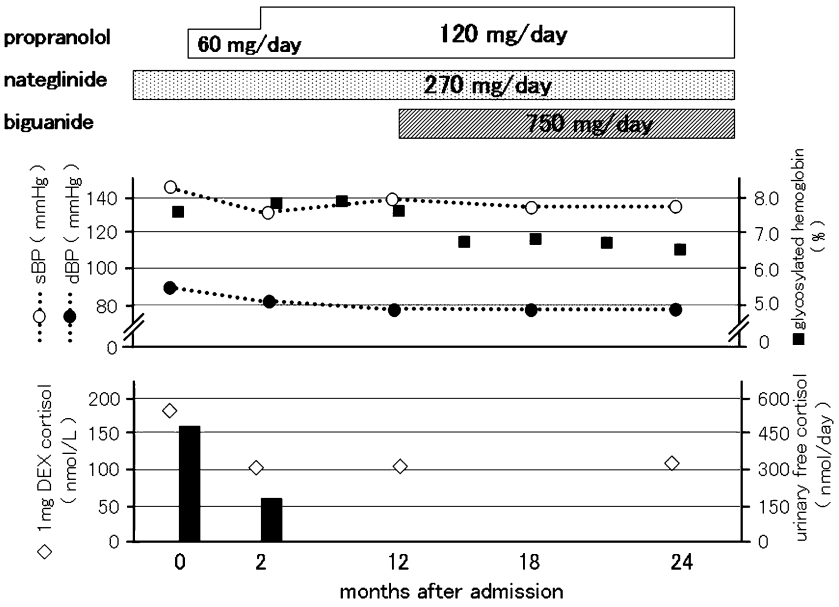

Fig. 4 Clinical course. Two months after the start of propranolol treatment, a decrease in the serum cortisol level in response to a low-dose DEX suppression test, a decrease in the urinary cortisol level, and a reduction in blood pressure were observed. Treatment with a biguanide (750 mg, daily) was initiated at 12 months after the start of propranolol treatment because the patient's glucose intolerance had not improved

Discussion

This patient was an extremely rare case of AIMAH with subclinical Cushing's syndrome, in whom the results of an upright test, and a catecholamine infusion test suggested catecholamine-dependent cortisol production, and the outcome of propranolol administration supported this conclusion. While propranolol treatment decreased cortisol secretion and improved the patient's blood pressure, no improvement in either the patient's diabetes mellitus or the tumor size was noted.

To our knowledge, this is the first report of AIMAH with subclinical Cushing's syndrome associated with the aberrant expression of β-adrenergic receptors, although a few cases of AIMAH with overt Cushing's syndrome induced by catecholamines have been previously reported [1–3]. Among the previously reported cases, only one patient responded to β-blockade, although a unilateral adrenalectomy was eventually performed because of an insufficient decrease in endogenous cortisol secretion [1]. Resection without attempting β-blockade was performed in the other cases [2, 3]. In contrast, our case did not exhibit Cushingoid features but had subclinical Cushing's syndrome, and β-blockade enabled a marked suppression of cortisol secretion in this patient. Interestingly, the urinary cortisol level, which is one of the most reliable markers of endogenous cortisol production, improved to within the normal range. The inhibition of cortisol secretion by propranolol was sustained for at least 24 months in this patient.

While the expression of β-adrenergic receptors has been observed in AIMAH as well as in adrenal adenoma or carcinoma, these receptors are not normally expressed in human adrenal cortex [1–3, 10, 11]. However, functioning receptors with the ability to bind to G proteins and stimulate cAMP-induced adenylate cyclase activity have been demonstrated in vitro only in tissue specimens from patients with AIMAH associated with β-adrenergic receptor expression [1–3]. Cortisol production via β-adrenergic receptors has also been confirmed in vivo [1–3]. Although the molecular mechanisms involved in the pathophysiology of AIMAH have not yet been fully recognized, the ectopic expression of β-adrenergic receptors resulting in the production of cortisol is suspected.

The changes in glucose metabolism were also investigated in the present patient to clarify the effects of β-blocker therapy. Hypercortisolism is apparently characterized by impaired insulin-dependent glucose uptake in the periphery and enhanced gluconeogenesis in the liver [12, 13]. Although propranolol treatment suppressed cortisol secretion in the present case, glucose metabolism did not improve. Whether an adrenalectomy or pharmacologic β-blockade is optimal for the treatment of AIMAH with subclinical catecholamine-induced Cushing's syndrome cannot be determined based on the results of only the present case; thus, additional cases or controlled studies are needed. Alternatively, a combination of subtotal adrenalectomy and β-blockade or metyrapone administration might also be useful.

Despite the suppression of cortisol secretion, propranolol treatment did not affect the metabolic abnormalities that were observed in the present case; various explanations for this apparent discrepancy are possible. First, ACTH reportedly accelerates cortisol production in patients with AIMAH [3, 4, 7]. Thus, ACTH blockade in combination with catecholamine stimulation might be important for an adequate reduction in cortisol secretion. Second, since the

effect of subclinical Cushing's syndrome on glucose metabolism remains unclear [8], insulin sensitivity should have been measured more precisely, such as using a glucose clamp study [14], in the present patient. Third, β-blockade could potentially reduce insulin secretion from pancreatic islet cells [15, 16]. Therefore, the effect of β-blockade on glucose metabolism might compete with the effect on the suppression of cortisol secretion.

Unexpectedly, the adrenal size did not change in the present case. In a previously reported case of AIMAH with LH-induced cortisol secretion, the size of the adrenal glands also did not change after 24 months of treatment, despite the complete suppression of LH secretion by leuprolide acetate [7]. Together, these results suggest that the suppression of endogenous ligands of abnormally expressed receptors or the administration of specific antagonists does not affect the tumor size.

In conclusion, we report the first case of AIMAH accompanied by subclinical Cushing's syndrome associated with the aberrant expression of β-adrenergic receptors. This patient was successfully treated with a β-blocker, which led to the suppression of cortisol oversecretion. Thus, β-blockade might be a potential therapeutic option for AIMAH accompanied by subclinical Cushing's syndrome associated with β-adrenergic receptor expression. Additional cases or controlled studies are needed to determine whether such treatment might be useful as a standard therapy.

References

1. A. Lacroix, J. Tremblay, G. Rousseau, M. Bouvier, P. Hamet, Propranolol therapy for ectopic beta-adrenergic receptors in adrenal Cushing's syndrome. N. Engl. J. Med. **337**, 1429–1434 (1997)
2. H. Mircescu, J. Jilwan, N. N'Diaye et al., Are ectopic or abnormal membrane hormone receptors frequently present in adrenal Cushing's syndrome? J. Clin. Endocrinol. Metab. **85**, 3531–3536 (2000)
3. N. Miyamura, A. Tsutsumi, H. Senokuchi et al., A case of ACTH-independent macronodular adrenal hyperplasia: simultaneous expression of several aberrant hormone receptors in the adrenal gland. Endocr. J. **50**, 333–340 (2003)
4. J. Bertherat, V. Contesse, E. Louiset et al., In vivo and in vitro screening for illegitimate receptors in adrenocorticotropin-independent macronodular adrenal hyperplasia causing Cushing's syndrome: identification of two cases of gonadotropin/gastric inhibitory polypeptide-dependent hypercortisolism. J. Clin. Endocrinol. Metab. **90**, 1302–1310 (2005)
5. D. Cartier, I. Lihrmann, F. Parmentier et al., Overexpression of serotonin4 receptors in cisapride-responsive adrenocorticotropin-independent bilateral macronodular adrenal hyperplasia causing Cushing's syndrome. J. Clin. Endocrinol. Metab. **88**, 248–254 (2003)
6. T. Mune, H. Murase, N. Yamakita et al., Ectopic overexpression of vasopressin v1a receptor in adrenocorticotropin-independent macronodular adrenal hyperplasia. J. Clin. Endocrinol. Metab. **87**, 5706–5713 (2002)
7. A. Lacroix, P. Hamet, J.M. Boutin, Leuprolide acetate therapy in luteinizing hormone–dependent Cushing's syndrome. N. Engl. J. Med. **341**, 1577–1581 (1999)
8. L. Tauchmanovà, R. Rossi, B. Biondi et al., Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J. Clin. Endocrinol. Metab. **87**, 4872–4878 (2002)
9. T. Suda, Preclinical Cushing's syndrome and adrenocorticotropic hormone-independent bilateral adrenocortical macronodular hyperplasia. Intern. Med. **36**, 601–602 (1997)
10. Y. Hirata, M. Uchihashi, S. Sueoka, S. Matsukura, T. Fujita, Presence of ectopic beta-adrenergic receptors on human adrenocortical cortisol-producing adenomas. J. Clin. Endocrinol. Metab. **53**, 953–957 (1981)
11. M.S. Katz, T.M. Kelly, E.M. Dax, M.A. Pineyro, J.S. Partilla, R.I. Gregerman, Ectopic beta-adrenergic receptors coupled to adenylate cyclase in human adrenocortical carcinomas. J. Clin. Endocrinol. Metab. **60**, 900–909 (1985)
12. N.R. Poa, P.F. Edgar, Insulin resistance is associated with hypercortisolemia in Polynesian patients treated with antipsychotic medication. Diabetes Care **30**, 1425–1429 (2007)
13. F. Fallo, A. Scarda, N. Sonino et al., Effect of glucocorticoids on adiponectin: a study in healthy subjects and in Cushing's syndrome. Eur. J. Endocrinol. **150**, 339–344 (2004)
14. M.E. Piché, S. Lemieux, L. Corneau, A. Nadeau, J. Bergeron, S.J. Weisnagel, Measuring insulin sensitivity in postmenopausal women covering a range of glucose tolerance: comparison of indices derived from the oral glucose tolerance test with the euglycemic-hyperinsulinemic clamp. Metabolism **56**, 1159–1166 (2007)
15. H. Mori, H. Ukai, H. Yamamoto et al., Current status of antihypertensive prescription and associated blood pressure control in Japan. Hypertens. Res. **29**, 143–151 (2006)
16. S. Bangalore, S. Parkar, E. Grossman, F.H. Messerli, A meta-analysis of 94, 492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. Am. J. Cardiol. **100**, 1254–1262 (2007)