Case Report

A Case of Primary Aldosteronism Due to Unilateral Adrenal Hyperplasia

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The case of a patient with primary aldosteronism due to unilateral adrenal hyperplasia (UAH) is reported. A 43-year-old man with an 8-year history of hypertension presented at our institution with hypokalemia, increased plasma aldosterone concentration (PAC), and suppressed plasma renin activity (PRA). An abdominal CT scan showed almost normal adrenal glands with slight enlargement in the left gland. ^{131}I-Norcholesterol adrenal scintigraphy under dexamethasone suppression showed bilaterally decreased uptake. To rule out idiopathic hyperaldosteronism, an adrenal vein sampling before and after ACTH stimulation was performed and a left-sided lateralization of PAC was observed. A left adrenalectomy was performed, and the patient had a good clinical and biochemical response. Micronodular hyperplasia was discovered in the adrenal gland histologically, and in the immunohistochemical analysis, positive staining for 3β-hydroxysteroid dehydrogenase in micronodular lesions confirmed the diagnosis of UAH. Although UAH is a rare subset of primary aldosteronism, it is surgically correctable as a unilateral autonomous aldosterone-producing lesion. Careful investigations, including bilateral adrenal vein sampling, should be performed for the diagnosis. (*Hypertens Res* 2005; 28: 379–384)

***Key Words*: hyperaldosteronism, unilateral adrenal hyperplasia, adrenal vein sampling, secondary hypertension**

Introduction

Most cases of primary aldosteronism (PA) belong to one of two subtypes, unilateral aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia (IHA), but some cases are classified into less common subtypes such as glucocorticoid responsive aldosteronism (*1*) and other familial forms (*2*). Rarely, PA is caused by unilateral adrenocortical hyperplasia (UAH). Indeed, Omura *et al*. (*3*) reported that the prevalences of APA, IHA and UAH were 4.9%, 1.2%, and 0.1% among 1,020 prospectively studied hypertensive outpatients. Since the first description, by Ross (*4*), of a case of PA caused by UAH, there have been at least 20 reported cases of PA caused by UAH (*5–17*). This rare cause of PA, which probably accounts for less than 1% of all cases of PA, usually mimicks unilateral adrenal adenoma, and is difficult to diagnose before resection. However, since all the previous cases of PA due to UAH have been surgically correctable with good clinical and biochemical response, it is important to determine unilaterality of aldosterone overproduction. The most reliable means of achieving this is to determine the aldosterone/cortisol ratio by adrenal vein sampling after ACTH stimulation (*18*).

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Received September 16, 2004; Accepted in revised form January 21, 2005.

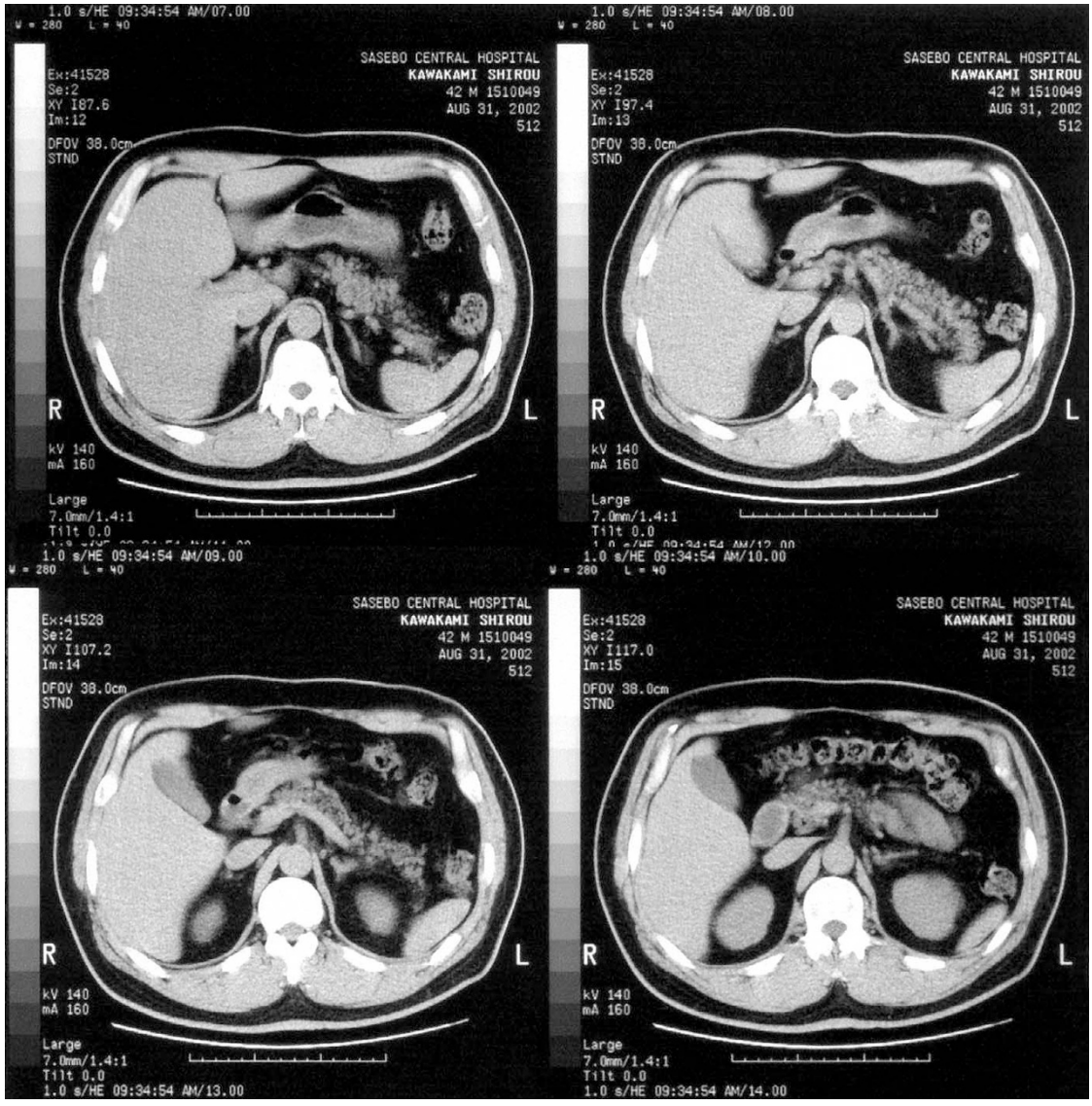

Fig. 1. *Abdominal CT scan showed almost normal adrenal glands with slight enlargement in the left gland.*

We report here the case of a 43-year-old man with persistent hypertension who presented with PA caused by UAH, which was diagnosed by adrenal vein sampling and successfully treated by unilateral adrenalectomy.

Methods

Measurement of plasma renin activity, serum cortisol, aldosterone, 18-hydroxycorticosterone, corticosterone and 11-deoxycorticosterone and urinary excretion of cortisol and aldosterone were performed by using radioimmunoassays. Blood samples were taken after 15 to 20 min of supine rest at 6:00–6:30 AM without sodium intake restriction (10–15 g of NaCl per day). The expression of steroidogenic enzyme, 3β-hydroxysteroid dehydrogenase, in the resected adrenal gland was examined by immunohistochemical staining as described previously (*19*).

Case Report

A 43-year-old man with an 8-year history of hypertension, which had previously been moderately controlled with several classes of antihypertensive drugs, visited the outpatient clinic of the Japan Self Defense Forces (JSDF) Hospital at Sasebo in May 2002. At the time of presentation at the clinic, he was being treated with 5 mg of enalapril maleate and 5 mg of amlodipine, and his blood pressure was 140/94 mmHg with hypokalemia (3.0 mEq/l). He did not have any history of weakness or numbness due to hypokalemia. His plasma aldosterone concentration (PAC) was elevated (35.2 ng/dl; reference value, 3.6 to 24.0) with suppressed plasma renin activity (0.3 ng/ml/h; reference value, 0.3 to 4.2) and excess urinary

Table 1. Clinical Data on 43-Year-Old Study Patient

Clinical tests	Preoperative values	Postoperative values	Reference values
Blood pressure (mmHg)	140/94	120/72	<130/<85
Plasma sodium (mEq/l)	144	143	135–150
Plasma potassium (mEq/l)	3.2	4.4	3.5–5.0
Plasma aldosterone (ng/dl)	17.3	4.6	2–13
Plasma renin activity (ng/ml/h)	0.2	0.5	0.2–2.7
Plasma cortisol (μg/dl)	17.4	12.2	<20
18-Hydroxycorticosterone (ng/dl)	46	5	1–7
Corticosterone (ng/ml)	13.5	2.22	0.38–8.42
11-Deoxycorticosterone (ng/ml)	0.52	0.12	0.08–0.28
Urinary aldosterone (μg/24 h)	10.3	0.9	<10
Urinary free cortisol (μg/24 h)	45.4	74	30–100
Urinary 17-hydroxycorticosteroids (mg/day)	3.5	8.4	2.9–11.6
Urinary 17-ketosteroids (mg/day)	2.6	7.2	4.6–16.4

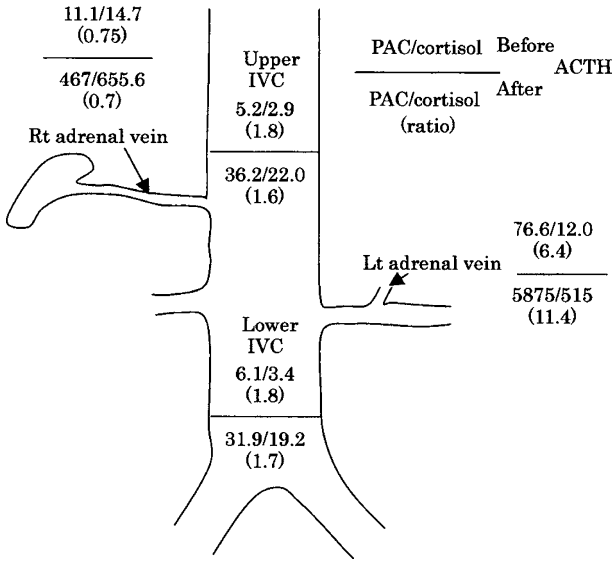

Fig. 2. *Adrenal vein sampling before and after ACTH stimulation. An adrenal vein sampling before and 30 min after ACTH stimulation (a constant infusion rate of 50 μg/h of cosyntropin) was performed and a substantial difference was noted between the left and the right adrenal glands. After ACTH stimulation, an aldosterone/cortisol ratio on the left adrenal gland increased from 6.4 to 11.4, whereas that on the right side remained the same (0.75 to 0.70).*

potassium excretion (74 mEq/day) in spite of the hypokalemia. His blood gas analysis showed mild metabolic alkalosis (pH 7.455, HCO_3^- 29.3 mEq/l, BE 5.6 mmol/l). Abdominal CT scanning showed almost normal adrenal glands with slight enlargement of the left gland (Fig. 1). His treatment with enalapril maleate and amlodipine was continued, and since a diagnosis of PA was suspected, spironolactone was added in a daily dose of 50 mg. In addition, he was referred to the JSDF Central Hospital for further examinations.

Before and after admission to JSDF Central Hospital, enalapril maleate and spironolactone had been stopped for more than 2 weeks to reevaluate his hormonal status, and potassium chloride 20 mEq was prescribed three times a day to stabilize his potassium levels. His PAC was 17.3 ng/dl with a PRA level of 0.3 ng/ml/h and an aldosterone/renin ratio of 57.7 (Table 1). The uptake of both adrenal glands was decreased in ^{131}I-norcholesterol adrenal scintigraphy after administration of 2 mg of dexamethasone for 14 days. Dexamethasone apparently reduced plasma ACTH, and both plasma and urinary cortisol with modest suppression in both plasma and urinary aldosterone (before/after: 17.3/9.0 ng/dl, 13.4/10.3 μg/g Cr). To rule out idiopathic hyperaldosteronism (IHA), an adrenal vein sampling before and 30 min after ACTH stimulation (a constant infusion rate of 50 μg/h of cosyntropin) was performed. A substantial difference was noted between the left and the right adrenal glands before ACTH stimulation. After ACTH stimulation, the aldosterone/cortisol ratio for the

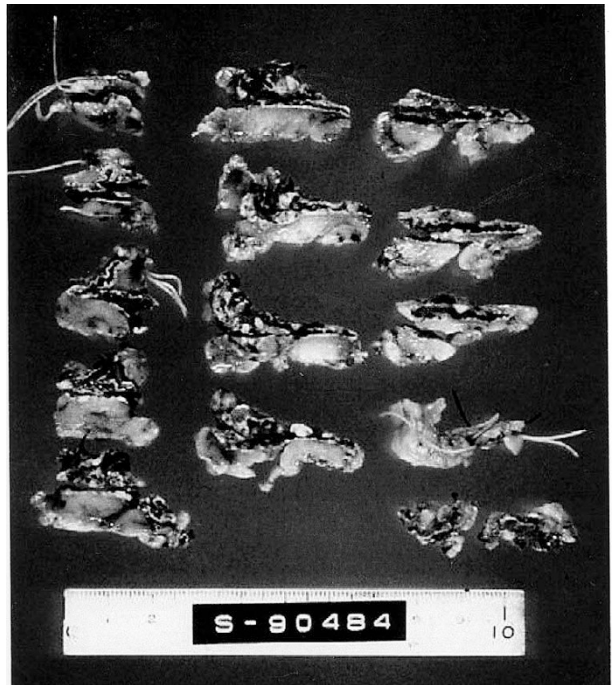

Fig. 3. *Multiple slices of the removed adrenal gland. The original size was 7.5×3.5×1.5 cm. There were some small macronodules (3–5 mm in diameter).*

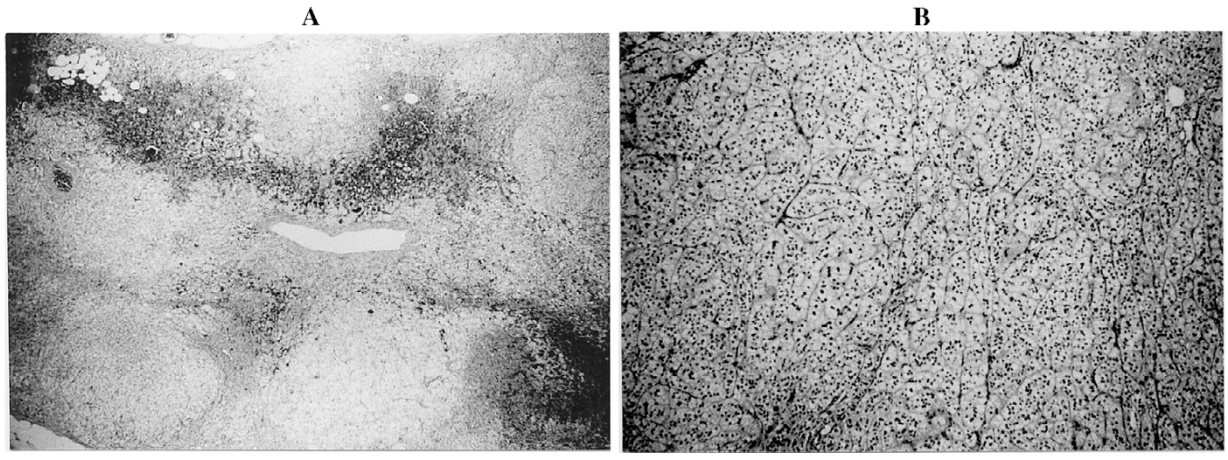

Fig. 4. *Histopathologic features of the removed adrenal gland. A: Low magnification view reduced from 20×. Diffuse micronodular adrenocortical hyperplasia was observed without capsulation. B: These micronodules almost all consisted of clear cells with abundant cytoplasm and polygonal nuclei, and are not encapsulated.*

left adrenal gland increased from 6.4 to 11.4, whereas that for the right side was not altered significantly (0.75 to 0.70) (Fig. 2). The findings at this point were consistent with unilateral disease, compatible with an APA. A left adrenalectomy by a lateral approach was then performed. The removed gland was 7.5×3.5×1.5 cm in size (Fig. 3). There were some small macronodular lesions (3–5 mm in diameter; arrow in Fig. 3). Diffuse micronodular adrenocortical hyperplasia was seen in the zona glomerulosa but not in the zona fasciculata or reticularis. The nodules were not encapsulated and the perinodular adrenal tissue was not atrophic (Fig. 4A). These micronodules were largely comprised of clear cells (Fig. 4B). Immunohistochemistry revealed abundant expression of 3β-hydroxysteroid dehydrogenase in micronodular lesions (Fig. 5) but not in the unaffected zona glomerulosa, which was consistent with paradoxical hyperplasia and excluded a diagnosis of IHA. Therefore, a diagnosis of micronodular adrenocortical hyperplasia was confirmed, compatible with UAH.

Ten days after surgery, PAC was 4.6 ng/dl, with concomitant decrease of intermediates such as 18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone and increase of PRA and serum potassium. The patient's blood pressure gradually decreased from 140/94 mmHg to 120/72 mmHg (Table 1). Follow-up over 12 months after adrenalectomy showed controlled hypertension, with the most recent reading being 120/70 mmHg on amlodipine 2.5 mg daily, and normokalemia.

Discussion

On initial assessment, the patient presented with typical primary aldosteronism including hypokalemia and hypertension, suppressed plasma renin activity and elevated plasma aldosterone level. Although serial CT scans showed mild hypertrophy of the left adrenal gland, ^{131}I-norcholesterol adrenal scintigraphy under dexamethasone suppression failed to show any abnormality of the adrenal glands. Indeed, the determination of the localization of PA by adrenal scintigraphy, CT scanning, and MRI remains limited (*20*–*22*). There are several reports that bilateral uptake (*22*) or no uptake (*23*) or even incorrect side uptake might occur in patients with proven aldosterone producing adenoma (*24*). For cases of unilateral adrenal hyperplasia, adrenal scintigraphy with or without dexamethasone treatment has been used in 8 cases with varying results: four had a bilateral uptake, 2 had the correct uptake, and 1 had early uptake on the correct side on day 3 followed by bilateral uptake on day 5 (*6*, *9*, *11*, *13*, *14*, *18*). In these cases, dexamethasone suppression did not improve the determination of the affected site. Based on these results and those of the present case, ^{131}I-scintigraphy appears not to be a reliable method to determine localization in patients with UAH.

Several trials have been conducted to determine whether or not patients with APA are surgically remedial. A fall in aldosterone or 18-hydroxycorticosterone in a postural stimulation test, preferably over 4 h (*25*), and bilateral adrenal vein sampling with the finding of a suppressed contralateral ratio (*i.e.*, <1) and/or a lateralized ratio exceeding 4–5 (*26*), seem to have been the most reliable methods. Furthermore, Yamahara *et al*. (*27*) reported that adrenal vein sampling under adrenocorticotropic hormone and angiotensin II receptor blocker can give a more accurate assessment of the aldosterone secretion. For the former procedure, among previously reported cases with UAH, 10 had a postural stimulation test, for which 5 were suppressed, 3 unchanged, and 2 had increased aldosterone levels. Although we did not perform the test in the present case, previous reports have suggested that UAH is autonomous from the renin-angiotensin system, and postural suppression of aldosterone or 18-hydroxycorticosterone alone is not a sufficient screening method for detecting UAH.

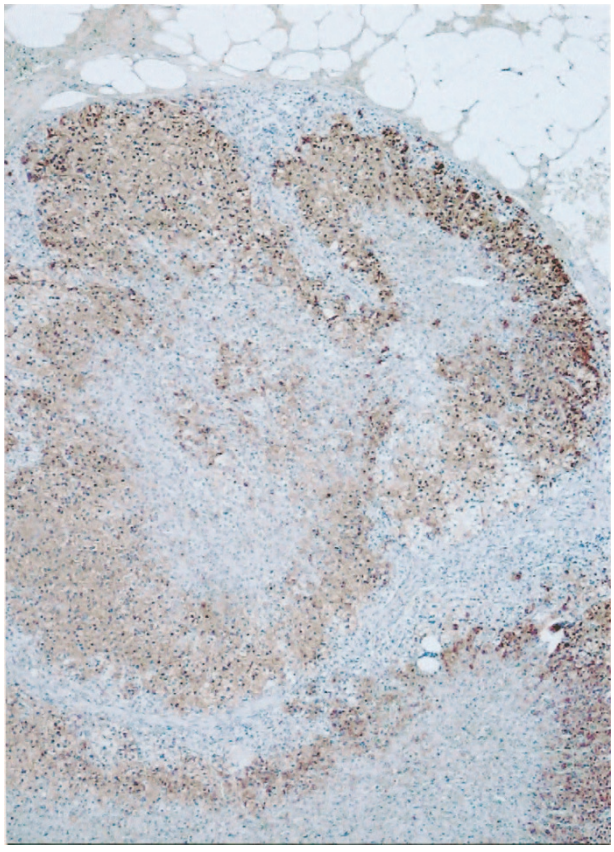

Fig. 5. *Immunohistochemistry of the removed adrenal gland. Abundant expression of 3β-hydroxysteroid dehydrogenase in micronodular lesions.*

Furthermore, although there are few data as yet, 18-hydroxycorticosterone levels do not seem to provide unambiguous discrimination between IHA and APA. For example, some reported cases had low levels (19.4 and 34 ng/dl respectively) (*15*, *28*), as did the present case (46 ng/dl), while other cases had higher levels exceeding 100 ng/dl (*29*). Therefore, neither the postural stimulation test nor measurement of 18-hydroxycorticosterone levels allows good discrimination between UAH and IHA.

For the procedure of bilateral adrenal vein sampling, exogenous ACTH stimulation of 50 μg/h is recommended (*30*, *31*), because misinterpretation occurred in the absence of ACTH stimulation (*25*) due to the pulsatile nature of aldosterone secretion in APA. Under ACTH stimulation, even a single vein approach (lateralized ratio >4–5 or contralateralized ratio <1), along with a positive posture test, might be sufficient to discriminate between bilateral adrenal hypertrophy and aldosterone producing adenoma (*29*). In previous reports of UAH, the bilateral adrenal vein sampling method was performed in 15 cases. Of these, 3 cases (*9*, *16*, *17*) were performed under ACTH stimulation and the PAC in the affected side was dependent of ACTH in all cases. Our case met both criteria with a lateralized ratio of 11.4 and a contralateralized ratio of 0.7 after ACTH stimulation, strongly suggesting a unilateral autonomous lesion.

Table 2. Hormonal Status of the Present Case with and without Dexamathasone Suppression

Clinical tests	Baseline value	Dexamathasone 2 mg	Reference values
ACTH (pg/ml)	70.6	3.9	<100
Plasma cortisol (μg/dl)	17.4	1.2	<20
Plasma aldosterone (ng/dl)	17.3	9.0	2–13
PRA (ng/ml/h)	0.2	0.3	0.2–2.7
Urinary creatinine (mg/24 h)	765	1,492	800–1,200
Urinary aldosterone (μg/24 h (μg/g Cr))	10.3 (13.4)	15.4 (10.3)	<10
Urinary free cortisol (μg/24 h (μg/g Cr))	45.4 (59.3)	24.9 (16.7)	30–100

PRA, plasma renin activity; Cr, creatinine.

Our patient's removed adrenal gland showed diffuse micronodular hyperplasia of the zona glomerulosa mainly consisting of clear cells without definite capsules or perinodular adrenal tissue atrophy. Histopathologic findings of removed adrenal glands in patients with UAH have not been consistent. Adrenocortical hyperplasia can be diffuse or nodular, and the diffuse disease is capable of conversion to nodular disease. This transformation is thought to be due to vascular changes and zones of local ischemia with compensatory hyperplasia, which may ultimately lead to nodule formation (*31*). In the present case, immunohistochemistry revealed abundant expression of 3β-hydroxysteroid dehydrogenase in micronodular lesions, which reconfirmed the diagnosis of UAH. Although immunohistochemistry has not been performed in any other reported cases of UAH, a functional determination could help in understanding the pathophysiology of the disease.

The surgical cure rate of 55% in UAH compares favorably with the 50–70% cure rate of APA (*32*, *33*). Because UAH is a rare but surgically remedial subset of APA, the diagnosis should be made by using selective adrenal vein sampling, especially in those patients who demonstrate apparent hyperaldosteronism and normal adrenal glands in standard imaging.

Acknowledgements

We gratefully acknowledge Dr. Seijiro Kado of the Department of General Medicine and Dr. Yutaka Kagata of the Division of Pathology, National Defense Medical College for providing pathologic evaluations of the adrenal tissue, and Setsu Suzuki at the Research and Laboratory Division of the JSDF Central Hospital for providing the radioimmunoassay analysis.

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