Primary aldosteronism with normal aldosterone levels in blood and urine

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Abstract. A 47 year old woman examined for hypertension (200/100 mmHg) was normokalaemic, and had low plasma renin activity (PRA) (0.1 ng/ml · h) and normal aldosterone levels in both plasma (7–13 ng/dl) and urine (4.7–7.4 µg/day). Computed tomography (CT) and scintiscan indicated an adenoma on the right adrenal gland, which was then removed. The histology of the adenoma and analysis of the aldosterone content were compatible with the criteria for an aldosterone-producing adenoma. Three months after surgery, her hypertension had improved, serum potassium levels had increased slightly, and PRA had normalized. This was an unusual form of primary aldosteronism which showed normal levels of aldosterone in both blood and urine.

Primary aldosteronism is usually recognized by hypertension, hypokalaemia, suppressed plasma renin activity (PRA), and hyperaldosteronism (Conn 1955). Variant forms have been reported however, e.g., normokalaemic (Conn et al. 1965; Bravo et al. 1983) and normotensive (Brooks et al. 1972; Snow et al. 1976; Zipser & Speckart 1978; Kono et al. 1981). In this report, we describe a variant form characterized by normal aldosterone levels in blood and urine.

Patient and Methods

A 47 year old woman suffering from nausea and vomiting was first documented as having hypertension (220/110 mmHg) on January 22nd, 1984. Her acute gastritis was cured and her hypertension was evaluated. She had no history of hypertension, weakness, polyuria, or nocturia. Her biochemical and hormonal data at clinic were as follows: serum potassium, 3.9 mEq/l; plasma renin activity (PRA), 0.2 ng/ml · h (normal: 0.5 to 1.5); plasma aldosterone concentration (PAC), 17.1 ng/dl (normal: 2.2 to 15); after an iv bolus of frusemide (40 mg) and 2 h standing, PRA was 0.6 ng/ml · h and PAC was 19.9 ng/dl. She was treated with labetalol (alpha and beta blocker, 50 mg 3 times daily) and nicardipine HCl (calcium antagonist, 20 mg 3 times daily), and her blood pressure was controlled at 154/90 mmHg.

She was hospitalized at our institute on March 28th, 1984, and kept on a constant 120 mEq sodium diet except on days of sodium-load. She continued the same medication as she had at clinic except on days of blood sampling for hormonal determinations. All blood samples for basal hormonal determinations were taken between 08.00 and 09.00 h. Physical examination was normal. Fundoscopic findings were almost normal (Scheie’s classification (Scheie 1953): H1 and S0). There were no findings suggesting cardiomegaly either on chest X-ray (cardiothoracic ratio: 45%) or electrocardiography. Her serum potassium levels (3.4 and 3.6 mEq/l) were in the low normal range (normal: 3.4–4.5). Urinary excretion of 17-hydroxycorticosteroids (5.3 mg/day) and 17-ketosteroids (7.4 mg/day) was normal. PRA was suppressed: 0.1 mg/ml · h. PAC was normal: 7.0 ng/dl at 08.00 h and 3.0 ng/dl at 20.00 h. Urinary aldosterone excretion (UAE) was also normal: 7.4 µg/day (normal: less than 10). After 3 days on a higher sodium diet (240 mEq/day), hormonal data showed no significant change, viz, PRA, < 0.1 ng/ml · h; PAC, 8.6 ng/dl; UAE, 7.6 µg/day. Fours hours standing after higher sodium diet increased PAC to 26.0 ng/dl and PRA to 0.1 ng/ml · h.

Selective adrenal vein catheterization obtained an adrenal vein aldosterone level higher on the right (3743.6 ng/dl) than on the left side (25.3 ng/dl). Venography
suggested the presence of an adenoma in the right adrenal gland. Computerized tomography (CT) indicated an adenoma on the right, but not on the left side. Adrenal scintiscan using 6β-iodomethyl-19-norcholest-5(10)-en-3ß-[131I](NCL-6-[131I]) (Nitta et al. 1976) was performed after dexamethasone administration (3 mg/day for 5 days prior to NCL-6-[131I] injection, followed by 2 mg/day for 7 days). Adrenal uptake of the radioimaging agent was relatively higher at the right (0.12% of the injected dose) than at the left gland (0.04%). To exclude the possibility that antihypertensive drugs interfered with hormonal levels, administration of drugs (labetalol and nicardipine HCl) was stopped for 3 days (a longer period off therapy could not be arranged because of her hypertension), before basal hormonal levels were determined. Results showed no significant change off therapy, viz, PRA, 0.1ng/ml·h; PAC, 13.3 ng/dl; UAE, 4.7 µg/day.

A right adrenalectomy was performed on May 23rd. A round adenoma (1.2 × 1.3 × 0.7 cm, 3.2 g) was found in the gland. The cut surface of the adenoma appeared yellow, typical for aldosterone-producing adenosomas (Fig. 1). The aldosterone content of the adenoma was 1.54 µg/g tissue. The patient was discharged on June 4th.

Three months after surgery, her hypertension had improved to 124/82 mmHg, although she still requires a reduced dose of medication (labetalol, 50 mg 3 times daily). Her serum potassium concentration increased to 4.1 mEq/l. PRA increased to 1.5 ng/ml·h and PAC remained in the normal range (10.5 ng/dl).

Aldosterone was measured by radioimmunoassay (RIA) as described elsewhere (Ogihara et al. 1977). Twenty-four hour urine was acidified by 0.2 n HCl to pH 1.0 for 18 h to enable measurement of both free and conjugated urinary aldosterone. Steroids in the adenoma were extracted by the method of Millington et al. (1974). The recovery, calculated by adding [125I]aldosterone, was 79.1%. PRA was measured using a commercial RIA kit purchased from Dainabot Radioisotope Laboratories, Tokyo, Japan.

**Discussion**

The excised adenoma was pathologically compatible with an aldosterone-producing adenoma (Conn 1955; Priestly et al. 1968). Kaplan et al. (1976) reported that the aldosterone content of such adenosomas ranged from 2.7 to 30.40 µg/g tissue (mean ± SD, 10.34 ± 9.46, n = 7), while that in 'normal' adrenal glands, in adenosomas from normotensive patients, and in adenosomas from patients with essential hypertension was less than 0.75 µg/g tissue (mean ± SD, 0.33 ± 0.18, n = 20). Saruta et al. (1980) also reported that the aldosterone content in
aldosterone-producing adenomas was 13.4 ± 5.3 µg/g tissue (mean ± SD, n = 10). Judging from available data, the aldosterone content in the adenoma described in our paper is relatively low compared to other aldosterone-producing adenomas, but notably higher than that in normal tissue. The adenoma not only produced aldosterone but also secreted this aldosterone into the adrenal vein, judged by the higher aldosterone level (14 times higher) on the adenoma side than on the opposite. Furthermore, this aldosterone secretion appeared to be autonomous because a high-sodium diet failed to suppress aldosterone levels in either blood or urine as Biglieri et al. (1967) reported. These findings indicate this to be an aldosterone-producing adenoma. The unique feature, however, is that our patient lacked some of the clinical features of primary aldosteronism which could be caused by an aldosterone-producing adenoma, viz. hyperaldosteronism and hypokalaemia. The serum potassium level in primary aldosteronism is dependent on sodium intake (Bravo et al. 1983), and normokalaemic primary aldosteronism is actually not very rare (Conn et al. 1965; Bravo et al. 1983). Primary aldosteronism with a normal aldosterone level, however, is very rare. Only Biglieri et al. (1967) and Channick et al. (1969) have reported cases of primary aldosteronism due to an aldosterone-producing adenoma with normal aldosterone excretion. The medication that our patient was taking (labetalol and nicardipine HCl) could possibly lower aldosterone levels in blood and urine. Some calcium blockers in particular, e.g., nifedipine, have been reported to lower PAC acutely in primary aldosteronism (Nadler et al. 1984). To eliminate such a possibility, we stopped the medication on the days blood samples were taken for hormonal evaluation. Thus, the period between blood sampling and drug administration (the last evening) was more than 12 h, which is much beyond the half-life of labetalol (less than 6 h) (Martin et al. 1978) and of nicardipine HCl (about 1 h) (Higuchi & Shiobara 1980). Furthermore, we observed that 3 days of off therapy did not cause any change in aldosterone levels in either blood or urine. Thus, it seems unlikely that such a drug effect was acting to lower aldosterone levels in blood and urine in this case.

Gross et al. (1983) reported that the adrenal uptake of the imaging agent (NCL-9) after dexamethasone treatment correlates significantly with urinary aldosterone excretion in patients with primary aldosteronism, suggesting that the uptake reflects the functional activity of an aldosterone-producing adenoma. Their conclusion was supported in our adrenal scintigraphy procedure: urinary aldosterone excretion correlated significantly with adrenal uptake on the adenoma side (r = 0.925, P < 0.01) in 6 cases which were all surgically confirmed to have aldosterone-producing adenomas (unpublished data). In the case described in this paper, adrenal uptake on the adenoma side was higher than that on the opposite side (0.12 vs 0.04%), but was the lowest of the 6 cases we have studied (n = 6, ranging from 0.13 to 0.86%). All results indicate that this aldosterone-producing adenoma had relatively weak activity and that it secreted comparatively less aldosterone, but sufficient to suppress renin secretion and to cause hypertension even though aldosterone levels remained within the normal range. The contribution of the adenoma to hypertension and suppression of renin is shown by the patient’s improvement after adrenalectomy.

This case demonstrates that, on rare occasions, primary aldosteronism can occur even without an obvious increase in aldosterone levels in the blood or urine and that physicians examining patients with low-renin hypertension may also need to check for primary aldosteronism.

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