A Case of Adrenal Tumor Producing Renin, Aldosterone, and Sex Steroid Hormones

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SUMMARY A 27-year-old woman with an adrenal tumor that produced renin and aldosterone, associated with hypertension and adrenogenital syndrome, is described. Severe hypertension, cardiomegaly, a low serum potassium level, clinical symptoms of adrenogenital syndrome, and a left upper abdominal tumor also were found. Endocrinological studies showed that plasma and urinary levels of sex steroid hormones such as dehydroepiandrosterone, androsterone, and testosterone were markedly increased. Plasma renin activity, plasma angiotensin II, and plasma aldosterone levels also were increased markedly, although deoxycorticosterone levels remained within the normal range. The possibility of renovascular hypertension was excluded by angiography of the renal artery and by venous sampling of plasma renin activity. Abnormal elevations in plasma aldosterone levels persisted despite normalization of plasma angiotensin II by converting enzyme inhibitor administration. It was suspected that this patient had an adrenal tumor producing renin as well as sex steroids and aldosterone. Microscopy of the resected tumor revealed that the tumor was composed mostly of cells with large nuclei and light cytoplasm. The tumor contained dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, aldosterone, and renin. Immunohistochemical study showed that some of the tumor cells produced renin. Biopsy of the left renal tissue showed evident atrophy of the juxtaglomerular cells and pronounced arteriosclerosis. After resection of the tumor, all blood and urinary levels of the abnormally increased hormones returned to a normal range and an apparent fall of blood pressure was noted. To our knowledge, this is the first report of a renin and aldosterone-producing adrenal tumor associated with hypertension and adrenogenital syndrome.

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KEY WORDS • renin-producing tumor • secondary hypertension • adrenogenital syndrome
• adrenal tumor

INITIALLY described by Robertson et al.1 and Kihara et al.2 as hypertension caused by a renal juxtaglomerular cell tumor, renin-producing tumors induce endocrinological hypertension through an overproduction of renin. More than half of the renin-producing tumors are renal in origin, and juxtaglomerular cell tumor is the most common. Few cases of nonrenal renin-producing tumors have been reported.3 To our knowledge, there have been no reports of a renin-producing tumor in which other hormones, including aldosterone, were simultaneously produced. Recently, we treated a patient with a renin-producing tumor originating from the left adrenal gland, which we believe is the first reported case of this type. The tumor simultaneously produced aldosterone and sex steroid hormones as well as renin. Clinically, this patient had severe hypertension complicated by adrenogenital syndrome.

Case Report

A 27-year-old woman was given a thorough medical examination for serious hypertension and virilism. She had experienced menarche at the age of 12 years, and the development of her secondary sex characteristics and subsequent menses were normal. Menstrual irregularity began in 1980, and amenorrhea developed in January 1983. A tendency toward hirsutism also was
seen. In March 1984, she was seen with palpitations, epigastric discomfort, and hypertension (190/106 mm Hg). Cardiomegaly was noted on chest roentgenogram. As medical treatment produced an insufficient fall in blood pressure, she was admitted to our department for further examination on June 1, 1984. Both parents had a history of hypertension, and her maternal grandmother had had diabetes and a myocardial infarction.

**General Examination**

On admission, the patient had a blood pressure of 210/106 mm Hg. Pulse rate was 81 beats/min and regular. The skin had a brownish tinge, and acne was found on her arms, chest, back, and legs. An elastic hard tumor, the size of a fetal head, was palpable in the left side of the upper abdominal area, but no vascular bruit was heard. Funduscopic examination revealed Grade III hypertensive retinopathy (Keith-Wagener-Barker classification). Gynecological findings included an increase of a malelike distribution of pubic hair, a swollen clitoris, and an atrophied uterus. Chest roentgenogram revealed cardiomegaly of 59% cardiothoracic ratio, and electrocardiographic findings also showed an apparent left ventricular hypertrophy. Peripheral hematological study revealed no abnormality, nor was any abnormality seen in liver function after biochemical examinations.

In five different measurements of serum electrolytes, low levels of serum potassium were revealed (mean, 3.3 ± 0.3 [SE] mEq/L; range, 3.0-3.8 mEq/L), but serum sodium levels were always within the normal range (mean, 139.2 ± 2.9 mEq/L; range, 135-143 mEq/L). A pronounced reduction in serum total cholesterol (37 mg/dl) and high density lipoprotein cholesterol (11 mg/dl) was found. Urinalysis revealed the presence of protein, 13.0 mg/dl, and urinary sediments contained 8 to 10 red blood cells and 6 to 8 white blood cells per high-power field.

A computed tomographic scan of the left-sided upper abdominal tumor showed a spherical tumor about 10.0 cm in diameter and a low density internal area in the upper portion of the left kidney (Figure 1). Both 67Ga and 131I-19-iodocholesterol scintigrams revealed remarkable uptakes of the isotope in the area corresponding to the tumor. Based on these results and on the clinical symptoms, this patient was considered to have adrenogenital syndrome caused by a malignant adrenal tumor.

**Endocrinological Examination**

To confirm the diagnosis and to determine the cause of her severe hypertension, endocrinological studies were conducted (Table 1). No abnormality was seen in pituitary and thyroid hormone levels, and no abnormal findings were revealed in the plasma levels of catecholamines determined by the method of Renzini et al. Among cortical hormones, abnormally elevated values were obtained for dehydroepiandrosterone (DHEA), androsterone, androstenedione, and testosterone. Although deoxycorticosterone levels remained within the normal range, a slight elevation was seen in corticosterone and cortisol. A pronounced elevation was observed in plasma aldosterone (ALDO). Both plasma renin activity (PRA) and plasma angiotensin II (ANG II) levels showed abnormal elevations. Urinary hormone levels revealed a pronounced increase in 17-ketosteroids and an apparent increase in 17-ketosteroid fractions such as androsterone, etiocholanolone, DHEA, and testosterone, as determined by gas chromatography. Urinary 17-hydroxycorticosteroid levels were normal.

The PRA was measured by the method of Haber et al., in which the PRA ranged from 0.3 to 2.80 (mean, 1.54 ± [SE] 0.12 ng of angiotensin I/ml/hr) in 34 normal subjects. Plasma ANG II and ALDO levels were measured by radioimmunoassay. The plasma ANG II levels in normal subjects were 12.2 ± 1.9 pg/ml (range, 2.5-21.3 pg/ml; n = 11), while plasma ALDO levels were 50.4 ± 0.2 pg/ml (range, 30-130 pg/ml; n = 91) in normal subjects. In these three hormone determinations, intra-assay and interassay errors were within 8%. All of the other hormones were measured by radioimmunoassay.

Based on the results of the endocrinological studies, adrenogenital syndrome was diagnosed; however, the hypertension of this patient was assumed to be caused by an activation of the renin-angiotensin system rather than by an abnormal increase of deoxycorticosterone as is commonly seen in patients with adrenogenital syndrome associated with hypertension. Therefore, to assess the possibility of renovascular hypertension, the following examinations were performed.

**Specific Examinations for Hypertension**

Angiography revealed no abdominal vessel stenosis within or outside the kidney. The PRA for each area examined by venous sampling during captopril admin-
Table 1. Endocrinological Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>35 pg/ml</td>
<td>—</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>4.4 ng/ml</td>
<td>—</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>8.1 mlU/ml</td>
<td>—</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>18.6 mlU/ml</td>
<td>—</td>
</tr>
<tr>
<td>Progesterone</td>
<td>1.3 ng/ml</td>
<td>—</td>
</tr>
<tr>
<td>DHEA</td>
<td>60 ng/ml</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>15 ng/ml</td>
<td>↑↑</td>
</tr>
<tr>
<td>Testosterone</td>
<td>319 ng/ml</td>
<td>↑↑</td>
</tr>
<tr>
<td>Estradiol</td>
<td>138 pg/ml</td>
<td>—</td>
</tr>
<tr>
<td>Deoxycorticosterone</td>
<td>0.216 ng/ml</td>
<td>—</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>16.7 mg/ml</td>
<td>↑</td>
</tr>
<tr>
<td>Cortisol</td>
<td>26.6 µg/dl</td>
<td>↑</td>
</tr>
<tr>
<td>Cortisone</td>
<td>24.8 mg/ml</td>
<td>—</td>
</tr>
<tr>
<td>11-OHCS</td>
<td>48.7 µg/dl</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>10.2 ng ANG I/ml/hr</td>
<td>↑↑</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>46.5 pg/ml</td>
<td>↑↑</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>523 pg/ml</td>
<td>↑↑</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>147.5 pg/ml</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>35.0 pg/ml</td>
<td>—</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-ketosteroid</td>
<td>223 mg/day</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Androsterone</td>
<td>29.1 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>Etocholanolone</td>
<td>46.3 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>DHEA</td>
<td>136.4 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>11-keto androsterone</td>
<td>1.32 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>11-keto etiocholanone</td>
<td>3.51 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>11-OH androsterone</td>
<td>4.93 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>11-OH etiocholanone</td>
<td>1.49 mg/day</td>
<td>↑</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&gt;201 mg/day</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>17-OHCS</td>
<td>6.8 mg/day</td>
<td>—</td>
</tr>
<tr>
<td>Vanillylmandelic acid</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone; OHCS = hydroxycorticosteroid; ANG I = angiotensin I; — = no change; ↑↑↑ = very large increase; ↑↑ = large increase; ↑ = moderate increase; ↑ = slight increase.

Vascular hyperreninemic hypertension caused by tumor-induced pressure was excluded. These results strongly suggested that the adrenal tumor was producing renin, which would explain the abnormally high blood renin level. On the other hand, it was also likely that the abnormally elevated plasma ALDO level was attributable to secondary aldosteronism caused by an increase in PRA or to aldosterone production by the tumor. Figure 2 shows the changes in PRA, plasma ANG II, and plasma ALDO levels after administration of captopril (75 mg/ml t.i.d. p.o.), an angiotensin I converting enzyme inhibitor. Following captopril administration, PRA showed a further, sustained increase, while plasma ANG II levels returned to the normal range. Despite normalization of plasma ANG II levels, an abnormal elevation in plasma ALDO persisted, suggesting that this elevation was not related to secondary aldosteronism but to aldosterone production by the tumor itself. Although blood pressure fell after administration of captopril, it remained in the hypertensive range.

Based on these results, we made a preoperative diagnosis that this patient had an adrenal tumor producing renin, sex steroid hormones, and aldosterone, with both renin and aldosterone contributing to the elevation in blood pressure. Tumor resection and left kidney biopsy were performed in our hospital on July 10, 1984.

Examination of Resected Tumor

The resected tumor was a capsulated, spherical mass that was 10 cm in diameter and weighed 950 g. The cut surface of the tumor was solid; however, some necrosis and bleeding were observed on the inferior side. Figure 3 shows light and electron microscopic findings. Light microscopy revealed that the tumor con-
sisted of many cells with eosinophilic, granular, and nonvacuolated cytoplasm. Some fat-laden cells were also observed. Both types of cells formed the trabecular or fasciculated structure. The stroma consisted of capillaries. Ultrastructurally, a lamellar arrangement of rough endoplasmic reticulum and tubular smooth endoplasmic reticulum was observed in the cytoplasm of tumor cells. Lipofuscin granules, lipid droplets, and intracytoplasmic microcytes with prominent microvilli were observed in some of the cells. Mitochondria were relatively large and oval, and some contained cristae similar to that seen in the tubulovesicular structure.

Morphology of the tumor cells indicated an adrenocortical cell origin. Based on the microinvasion of tumor cells into the capsule, moderate cellular atypism, and the presence of necrosis in the tumor mass, this tumor was classified as an adrenocortical carcinoma with low-grade malignancy. The following list shows the results of endocrinological studies on tumor tissue, as measured by radioimmunoassay:

- Desoxycorticosterone: 4.59 ng/g wet weight
- Testosterone: 52.4 ng/g wet weight
- DHEA: 6385 ng/g wet weight
- DHEA sulfate: 1572 ng/g wet weight
- Cortisol: 244 ng/g wet weight
- Aldosterone: 1.73 ng/g wet weight
- Active renin: 225.7 μg/g wet weight
- Total renin: 421.6 μg/g wet weight
- Renin (by direct radioimmunoassay): 5.3 μg/g wet weight

Active renin concentration, and total renin concentration, were all apparently elevated compared with the renin levels in the renal cortex. The renin content in the tumor tissue was similar to or higher than that reported in extrarenal renin-producing tumors. The incubation of tumor tissue extract also showed little or no angiotensin I production. When incubated with an adequate amount of substrate for renin, however, extremely high renin activity was confirmed. These findings indicate that the tumor produced only renin with no substrate production for renin. The renin in the tumor tissue was found to be present at a high concentration by direct radioimmunoassay, which is specific for human renin. Thus, the enzyme with renin activity detected in the tissue extract was also proven to be a true renin in terms of enzyme protein. The total renin activity determined after treatment with trypsin was about twofold higher than before treatment. From this observation it was surmised that the tumor probably produced prorenin, which is converted to active renin in tissue or blood. The biopsy specimen of the left renal tissue showed atrophy of the juxtaglomerular cells and pronounced arteriosclerosis. In addition, inflammatory cell infiltration was observed in the renal parenchyma, suggesting the presence of pyelonephritis.

After resection, blood levels of sex steroid hormones, corticosterone, and aldosterone and urinary 17-ketosteroid levels, which had shown abnormal elevations preoperatively, were all normalized to 1.37 mg/ml, 168.4 pg/ml, and 0.12 mg/day, respectively. Moreover, PRA was also restored to its normal level (2.28 ng angiotensin I/ml/hr).

Blood pressure did not completely return to the normal range, although it did decrease from 184 ± 29/110 ± 12 mm Hg (mean values of 3 measurements; no antihypertensive therapy) 1 week before operation to 165 ± 11/102 ± 7 mm Hg 1 week after the operation (no therapy). On the basis of these results, coupled with the family history, complication of essential hypertension cannot be excluded at the present time. Signs of masculinization, such as hairy limbs and swollen clitoris, gradually improved.
Discussion

In a search of the literature, we found 39 cases of renin-producing tumor. Of these, juxtaglomerular cell tumor was the most frequent, accounting for 24 cases. The remaining eight patients had other types of renal tumor. An extrarenal renin-producing tumor is extremely rare. The seven reported cases consist of two cases of lung cancer, one case of liver teratoma, one case of orbital vessel epithelial cell tumor, one case of pancreatic cancer, one case of bladder cancer, and one case of malignant tumor of the juxta-ovarian tissue. To our knowledge, a renin-producing tumor originating from the adrenal has not been reported previously, and the present report is the first such case of a renin-producing adrenal tumor. It was shown recently, however, that renin-producing cells are also present in the adrenal cortex. The fact that the adrenal tumor in our patient produced renin indicates a malignant tumorous change of renin-producing cells.

When making a differential diagnosis of severe hypertension associated with hyperreninemic hyperaldosteronism, malignant hypertension and renovascular hypertension should be considered. Based on renal function, ocular findings, blood pressure, and clinical symptoms, malignant hypertension was excluded in our patient. No stenosis of renal arteries including branches was detected by renal angiography in our patient, nor was a remarkable elevation in PRA seen in samples collected from the left renal vein. In addition, the biopsy specimen of renal tissue showed atrophy of juxtaglomerular cells. From these findings, the possibility of increased renin production in the kidney on the affected side was ruled out. Moreover, augmented production and secretion of renin by the contralateral kidney or other sites were unlikely since blood pressure fell and both PRA and plasma ALDO became normal postoperatively in this patient. Therefore, increased renin production was considered to occur within the tumor itself. In fact, in this patient a large amount of renin was contained in the tumor, and localization of renin in the tumor was also confirmed by a specific immunohistochemical method. With respect to secretory behavior of the renin produced in our patient's tumor, plasma ANG II was decreased and normalized following administration of captopril; this effect was accompanied by a rapid elevation in PRA. These findings indicate that activation of either a short feedback mechanism through ANG II or a baroreflex mechanism by decreasing blood pressure (or both) are involved in the production and secretion of renin by the tumor. In renin-producing tumors reported previously, no conclusion was made as to whether the renin produced by tumors is self-limiting. On the other hand, the local distribution pattern of renin within the tumor in our patient indicates a mechanism by which tumor cells produce prorenin. These findings are in agreement with the results obtained by Mimran et al., who reported that inactive renin is present within the tumor.

In our patient, it was difficult to regard overproduction of mineralocorticoids as the only factor responsible for pathogenesis of hypertension because of the high level of PRA. Thus, a disease entity related to activation of the renin-angiotensin system was considered. In addition, the finding that the elevation in plasma ALDO persisted even after normalization of plasma ANG II by administration of captopril led to the preoperative diagnosis of ALDO overproduction by the tumor itself. Postoperatively, this diagnosis was confirmed through the existence of ALDO in the tumor.

To our knowledge, none of the renin-producing tumors described previously were reported to produce hormones in addition to renin. Thus, the present case is considered to be extremely rare in that the tumor produced various hormones such as aldosterone and sex.
steroid hormones simultaneously with renin. We believe that the present report is the first of this type and therefore offers information of value for future investigations.

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