Endocrine, *vol. 21, no. 3, 221–226, August 2003* 0969–711X/03/21:221–226/$25.00

A Case of Normoreninemic Aldosterone-Producing Adenoma Associated with Chronic Renal Failure

Case Report and Literature Review

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The diagnosis of aldosterone-producing adenoma (APA) is challenging for endocrinologists, as APA does not always present with the typical constellation of clinical and laboratory features, such as hypertension, hypokalemia, suppressed plasma renin activity (PRA), and high plasma aldosterone concentration (PAC). Very recently, several studies have indicated that APA can be discovered even in normokalemic subjects with normal PRA more frequently than previously considered. Here we report a case of APA associated with chronic renal failure, which showed normokalemia and normal PRA. The patient was referred to our clinic for evaluation of an incidentally discovered adrenal mass with abnormally high PAC. After 6 yr, it was found that the right adrenal tumor showed a marked increase in size. Endocrinological examinations indicated normal PRA and markedly high PAC. Aldosterone showed a better response to the upright posture test than that to ACTH stimulation test. The diagnosis of APA was made based on the markedly high PAC to PRA ratio and the adrenocortical scintigraphy, which showed unequivocal uptake into the tumor. Right laparoscopic adrenalectomy was performed, revealing a right adrenocortical adenoma with massive hemorrhage. Histopathological examinations revealed the presence of two independent adrenocortical adenomas, one APA with predominant clear tumor cells and few c17 (17alpha-hydroxylase) immunoreactivity and the other, cortisol producing adenoma with compact cytoplasm and abundant C17 immunoreactivity. This case indicates a difficulty of diagnosis of "normoreninemic APA" with renal failure. This case is in line with the recent concept that APA is a continuous condition in which only a minority of patients have the classical clinical picture of primary aldosteronism such as hypokalemia. It is possible that normokalemic APA constitutes the most common presentation of the disease.

Key Words: Primary aldosteronism; chronic renal failure; plasma renin.

Introduction

A typical clinical constellation of primary aldosteronism caused by aldosterone-producing adenoma (APA) is hypertension and hypokalemia, which is associated with suppressed plasma renin activity (PRA) and high plasma aldosterone concentration (PAC) *(1,2)*. However, very recently, several studies have indicated that APA can be discovered even in normokalemic subjects with normal plasma renin more frequently than previously considered in both Caucasians and Asians *(2–5)*. Those studies may call attention to Conn's earlier recommendation that every patient with "essential hypertension" should undergo appropriate testing to exclude APA even in the absence of hypokalemia *(3)*.

Furthermore, a few cases with APA associated with chronic renal failure have been reported, in which PRA was normal or even high *(1,6–9)*. Here we report a case of normoreninemic and normokalemic APA under hemodialysis therapy, which showed a rapid growth during follow-up for 6 yr. Pitfalls will be discussed in diagnosis of APA with chronic renal failure, and the possible involvement of renin–angiotensin system in the tumor development will be also mentioned.

Case Report

In June 1997, a 63-yr-old woman was referred to our endocrinology clinic by nephrologists (H.K., E.O., and A.H.) seek-

Received March 26, 2003; Revised April 21, 2003; Accepted April 28, 2003.

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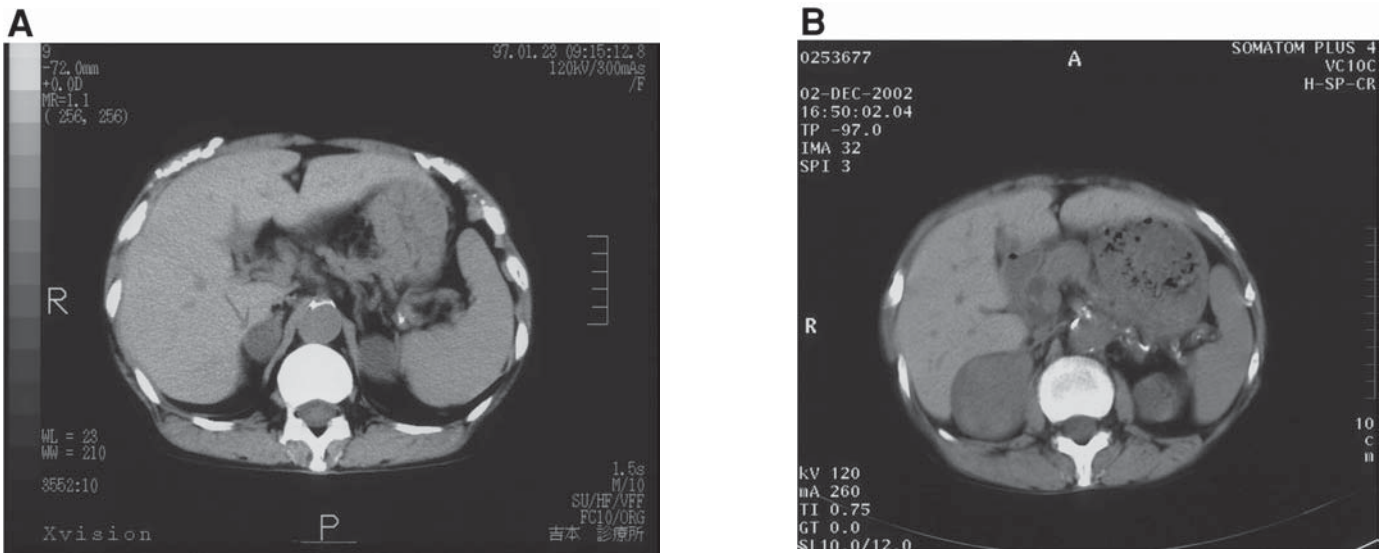

Fig. 1. The computed tomography (CT) of the abdomen performed in 1997 (left panel) and in 2002 (right panel). The right adrenal tumor, as shown in arrows, showed a rapid growth.

ing further examinations of the right adrenal mass of 2 cm, which was incidentally found by abdominal ultrasonography. She had been under hemodialysis therapy for 6 yr under the diagnosis of chronic renal failure caused by chronic glomerulonephritis with malignant hypertension. The diagnosis of chronic glomerulonephritis and malignant hypertension had been made based on the findings of renal biopsy and the rapid deterioration of renal function, respectively. Her blood pressure was high (164/68 mmHg) after the introduction of hemodialysis, but no antihypertensive agent was given. The retinal examination was not performed. Therefore, the diagnosis of malignant hypertension was considered to be inappropriate. Her serum potassium level was normal (4.8 mEq/L), but showed abnormally high PAC (21,900 pg/mL) and normal PRA (3.94 ng/mL/h). Although the radiologist, who performed computed tomography (CT), as shown in Fig. 1 (left panel), suggested a possibility of renal cyst rather than adrenal tumor, a possibility of nonfunctioning adrenal tumor could not be excluded. It was decided that she would be followed up with a regular check-up using imaging studies, because the thorough endocinological examinations required admission, and the results might be influenced by renal failure and hemodialysis, necessitating complex evaluations. Antihypertensive agents were administered (losartan 25 mg/d and thereafter changed to amlodipine 2.5 mg/d). In September 1998, she was referred to our clinic again, and the magnetic resonance imaging study showed an enlargement of right adrenal mass of 3 cm in diameter. However, the diagnosis of nonfunctioning adrenal adenoma was considered to be more likely than APA. Thereafter, she dropped out from regular visits to our clinic.

In November 2002, she was referred to our clinic again because the computed tomography indicated that the right adrenal mass showed a remarked increase in diameter from 3 to 6 cm (Fig. 1, right panel).

The patient was admitted and the endocrinolgical examinations were performed (Table 1A). Basal PRA and PAC levels were 1.2 ng/mL/h and 32,000 pg/mL, respectively, resulting in a PAC to PRA ratio of 26,670. The upright posture test evoked a marked response of PAC (29,000–75,000 pg/mL), which was not typical to APA *(9)*. Overnight dexamethasone suppression test (dexamethasone 2 mg po) resulted in normal suppression of serum cortisol, but no change in PAC. Both serum cortisol and PAC showed circadian variations, whereas ACTH did not show any significant circadian rhythm. Synthetic 1-24 ACTH administration (0.25 mg iv) evoked a normal increase in cortisol (11.2 to 25.8 μg/dL) and an increase in aldosterone (32,000 to 37,000 pg/mL). Adrenal scintigraphy with [^{131}I]iodomethyl-19-norcholesterol after dexamethasone (2 mg/d po, for 7 d) clearly indicated uptake into the adrenal tumor (Fig. 2). The diagnosis of APA was made based on both the adrenal scintigraphy and the unequivocally high ratio of PAC to PRA *(9)*. Right laparoscopic adrenalectomy was performed. Histopathological examinations (Fig. 3) revealed the presence of two independent adrenocortical adenomas. Both of these tumors were encapsulated and well-circumscribed and were diagnosed as benign adenomas based on the criteria of Weiss *(10)*. One was composed of predominant clear tumor cells and the other was composed of predominantly compact tumor cells. The former tumor was associated with hyalinized degeneration possibly due to ischemic changes and the latter tumor was associated with myelolipomatous degeneration. Immunoreactivity of steroidogenic enzymes was detected in both types of tumors, but C17-positive tumor cells were markedly sparse in the former. The attached non-neoplastic adrenal

Table 1

A. Endocrinological Examinations Before the Operation

Circadian rhythm	12 AM	5 PM	10 PM	8 AM
PRA (ng/mL/h)	1.4	1.7	1.1	1.2
PAC (pg/mL)	23,000	11,000	7560	32,000
ACTH (pg/mL)	15.6	20.3	27.5	33.2
Cortisol (ng/mL)	7.2	5.5	5.1	11.2
Rapid ACTH test	0	30	60 (min)	
PRA (ng/mL/h)	1.2	1.3	1.1	
PAC (pg/mL)	32,000	35,000	37,000	
Cortisol (ng/mL)	11.2	17.2	25.8	
Upright posture test	0	30	60 (min)	
PRA (ng/mL/h)	2.8	3.1	3.2	
PAC (pg/mL)	29,000	53,000	75,000	

Overnight dexamethasone suppression test (dexamethasone 2 mg po)	before	after
PRA (ng/mL/h)	1.2	1.7
PAC (pg/mL)	32,000	31,000
ACTH (pg/mL)	33.2	<4.0
Cortisol (ng/mL)	11.2	2.6

B. Time-Course Change in Endocrinological Data and Imaging Studies

Month/Day/Year	PRA (ng/mL/h)	PAC(pg/mL)	Plasma potassium level (mEq/L)	Diameter of the tumor (imaging method)[a]
2/7/97	3.94	21,900	4.8	2.5 cm (US)
9/12/97	5.14	7380	4.0	
12/5/97	2.12	16,900	4.5	
9/10/98	2.00	14,900	4.0	3 cm (MR)
11/27/02	1.4	23,000	5.0	5.5–6 cm (CT & MR)
1/6/03	3.0	202	4.4	—

C. Circadian Rhythm

Circadian rhythm	8 AM	5 PM	10 PM
PRA (ng/mL/h)	3.0	2.3	2.5
PAC (pg/mL)	202	186	200
ACTH (pg/mL)	42.0	13.0	4.0
Cortisol (ng/mL)	10.2	7.1	1.6

[a]US, ultrasound; MR, magnetic resonance; CT, computed tomography.

gland demonstrated a mild degree of cortical atrophy in the zona fasciculata and reticularis and hyperplasia in the zona glomerulosa, in which 3-beta-hydroxysteroid dehydrogenase immunoreactivity was detected.

After the operation, her serum potassium level remained within normal limits, but still required the administration of amlodipine (2.5 mg/d) to maintain normal blood pressure. The postoperative endocrinological examinations showed a decrease in PAC (202 pg/mL), whereas PRA showed a tendency of increase (from 1.4 to 3.0 ng/mL/h), as shown in Table 1B. This increase in PRA was probably explained by two mechanisms; first, PRA escaped from the suppression by the autonomously secreted aldosterone, and second, the stimulation of PRA by chronic renal failure, i.e., secondary aldosteronism became to be more manifest. Furthermore, both ACTH and cortisol showed normal circadian rhythm, but PAC did not show circadian variation anymore (Table 1C).

Discussion

The diagnosis of APA in subjects with chronic renal failure is challenging for endocrinologists, as they do not always present with the typical constellation of clinical and laboratory features of APA. PRA can escape suppression in APA complicated by chronic renal failure *(1)*. Therefore, nor-

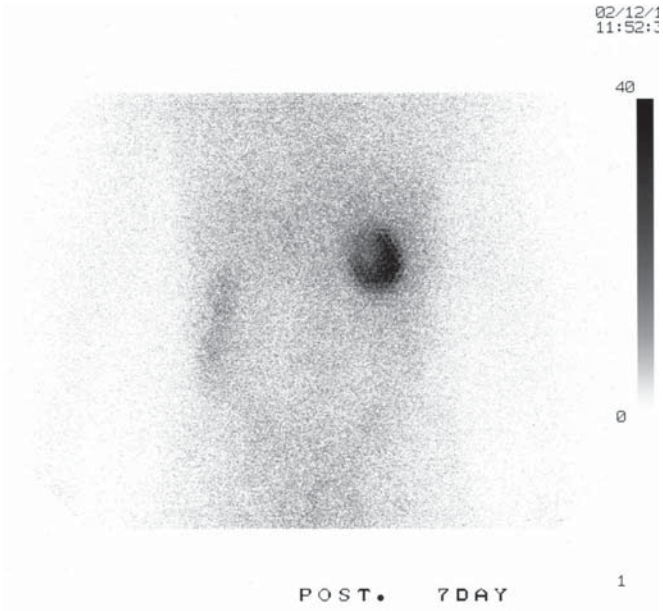

Fig. 2. Result of adrenal scintigraphy using [^{131}I]iodomethyl-19-norcholesterol (posterior to anterior view). Dexamethasone (2 mg/d, po, 7 d) was administered before the scintigraphy. It clearly indicated uptake into the right adrenal tumor.

mal levels of PRA, serum potassium, or blood pressure do not exclude the diagnosis of PRA in chronic renal failure *(1)*. To our knowledge, only five cases of APA with chronic renal failure have been reported in the English literature *(1,6–9)*, as shown in Table 2. Despite markedly high PAC, hypokalemia was found in only one case *(9)*. Although PAC is known to be high in chronic renal failure *(12–14)*, the PAC in the cases with APA is generally higher than those in subjects of renal failure without APA. Furthermore, PAC to PRA ratio, which has been established as a good index for screening APA *(5,12)*, seems to be also valid in subjects with renal failure.

Although APA is generally a small lesion, usually less than 2 cm in diameter *(15)*, the tumor of the present case was as large as 6 cm in diameter. In general, APA may exist for many years before hypokalemia develops, as Conn suggested earlier *(1,3)*. The renin–angiotensin system (RAS) has recently been indicated as playing an important role in cell growth, including the growth of adrenocortical cells *(16,17)*. The present case of APA showed circadian rhythm of PAC. PAC showed a better response to the upright posture test than to rapid ACTH stimulation, suggesting dependency of aldosterone to AII (AII) rather than to ACTH. This pattern was, although not typical to APA, previously reported in several cases of APA *(15)*, and might reflect hypersensitivity of AII *(17)*. In this context, it is possible, although there is no definite evidence, that the activation of RAS may have acted to promote tumor growth in this case. However, as discussed below, the massive bleeding in the tumor may have also been involved in the rapid growth of the tumor. The patient was introduced with hemodialysis based on the diagnosis of malignant hypertension. However, it is possible that APA did exist at that time. APA is less likely complicated with vascular damage or malignant hypertension *(8)*, and the diagnosis of malignant hypertension was not substantiated in this case.

The present case was associated with a mild degree of paradoxical hyperplasia of the zona glomerulosa, which was generally detected in non-neoplastic adrenal glands of the cases with APA *(18)*. The expression of dehydroepiandrosterone-sulfate transferase (DHEA-ST), which is one of the hallmarks to reflect hypothalamo-pituitary-adrenal (HPA) axis, was decreased in the zonae fasciculata and reticularis of the attached non-neoplastic adrenal gland. The immunoreactivity of 3-beta-hydroxysteroid dehydrogenase (3-β-HSD) was not usually detected in these hyperplastic glomerulosa cells. However, in this case, an abundant expression of 3-β-HSD in hyperplastic zona glomerulosa of the attached adrenal gland might be consistent with an activation of RAS in this particular case.

As for treatment, surgical therapy is not always best for the APA with chronic renal failure *(9)*. Low plasma renin status is generally considered to protect against vascular injuries of hypertension through suppressed AII production *(8)*. Therefore, vascular complications may be more frequent. Therapy in subjects with APA with renal failure, which escapes suppression of PRA, than those without it. The present case was accompanied by massive hemorrhage, at least partly caused by bleeding tendency associated with renal failure. On the other hand, unless surgical treatment was performed, the unsuppressed RAS activation may have promoted the tumor growth further. It therefore remains to be

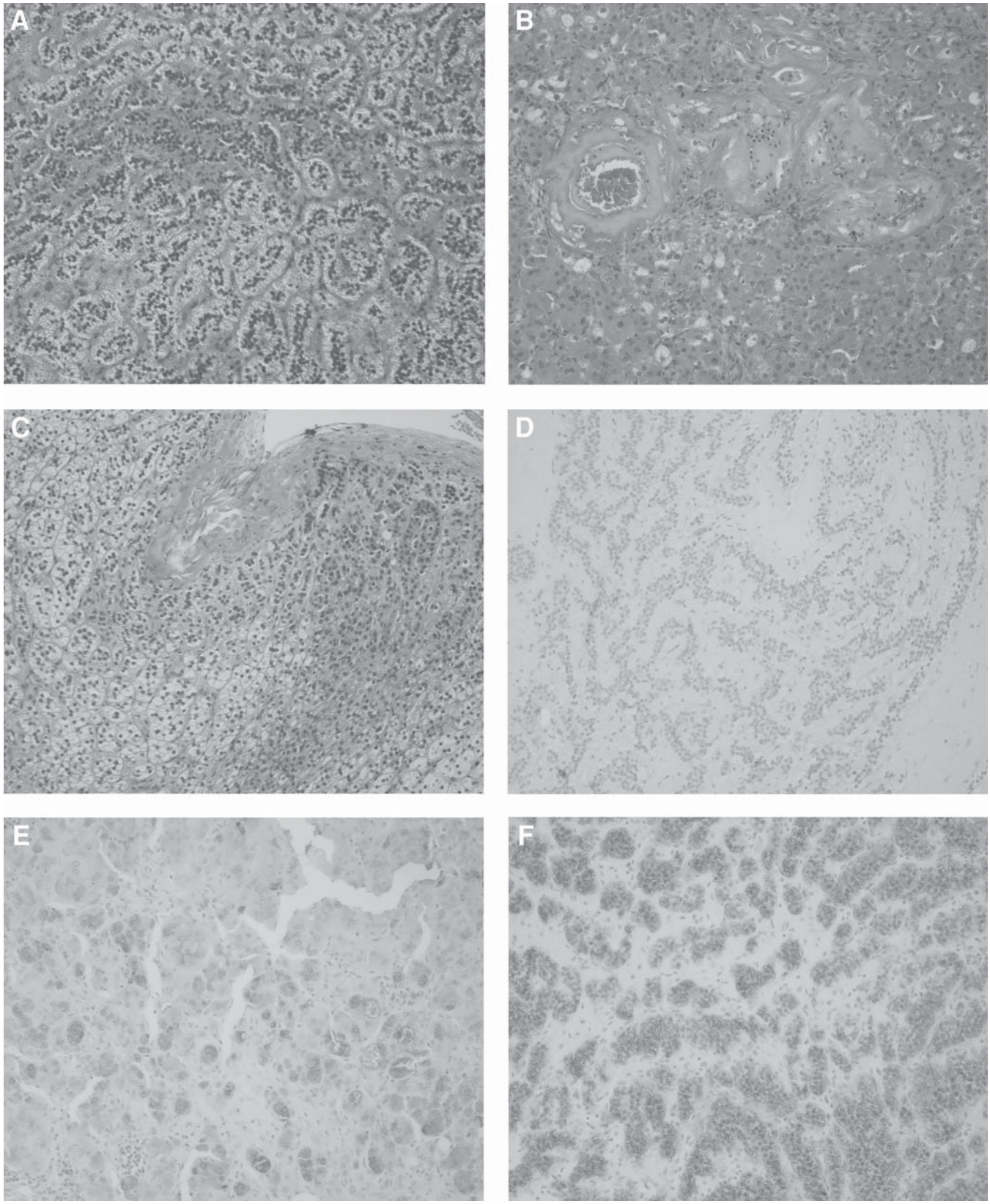

Fig. 3. Pathological examinations of the resected tumor specimen. Histopathological findings of clear tumor cells (**A**), compact tumor cells (**B**), and attached non-neoplastic adrenal gland (**C**). Immunohistochemistry of C17 in clear tumor cells (**D**), in compact tumor cells (**E**), and immunohistochemistry of 3-beta-hydroxysteroid dehydrogenase (**F**).

Table 2
Reported Cases of APA Associated with Chronic Renal Failure

	PRA[a] (ng/mL/h)	PAC (pg/mL)	Plasma potassium level (mEq/L)	Diameter of the tumor	Therapy
Nakada et al. *(6)*	1.9–2.3	370–470	normal	3↔3↔3.5 cm	operated
Matsuda et al. *(7)*	1.409	910	3.1	2.5 cm	not operated
Oka et al. *(8)*	(122 pg/mL)[b]	252	3.1	2↔1.5 cm	operated
Ito et al. *(9)*	0.7	300	2.9	2 cm	not operated
Oelkers et al. *(1)*	2.2	n.m.	3.4–4.1	1.3 cm	operated
The present case	1.2	32,000	4.0	6 cm	operated

[a]APA, aldosterone-producing adenoma; PRA, plasma renin activity; PAC, plasma aldosterone concentration; n.m., not measured.
[b]Active renin concentration.

elucidated whether operation is the best therapy for the APA with chronic renal failure.

In summary, we reported a case of "normoreninemic" APA associated with renal failure, which showed rapid growth of the tumor. Because APA with renal failure may be easily overlooked, subjects under hemodialysis should be screened for APA, even in the absence of hypertension, hypokalemia, or suppressed PRA. This case is in line with the recent concept that APA is a continuous condition in which only a minority of patients have the classical clinical picture of primary aldosteronism such as hypokalemia and hypertension. It is possible that normokalemic APA constitutes the most common presentation of the disease *(2,4,15)*.

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