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*Case Report*

# A Case of Aldosterone-Producing Adenoma with Severe Postoperative Hyperkalemia

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TANIGUCHI, R., KOSHIYAMA, H., YAMAUCHI, M., TANAKA, S., INOUE, D., SATO, Y., SUGAWA, A., MURAMATSU, Y. and SASANO, H. *A Case of Aldosterone-Producing Adenoma with Severe Postoperative Hyperkalemia.* Tohoku J. Exp. Med., 1998, **186** (3), 215-223 —— It is known that some patients with primary aldosteronism show postoperative hyperkalemia, which is due to inability of the adrenal gland to secrete sufficient amounts of aldosterone. However, hyperkalemia is generally neither severe nor prolonged, in which replacement therapy with mineralocorticoid is seldom necessary. We report a case of a 46-year-old woman with an aldosterone-producing adenoma associated with severe postoperative hyperkalemia. After unilateral adrenalectomy, the patient showed episodes of severe hyperkalemia for four months, which required not only cation-exchange resin, but also mineralocorticoid replacement. Plasma aldosterone concentration (PAC) was low, although PAC was increased after rapid ACTH test. Histological examination indicated the presence of adrenocortical tumor and paradoxical hyperplasia of zona glomerulosa in the adjacent adrenal. Immunohistochemistry demonstrated that the enzymes involved in aldosterone synthesis, such as cholesterol side chain cleavage (P-450$_{scc}$), 3$\beta$-hydroxysteroid dehydrogenase (3$\beta$-HSD), and 21-hydroxylase (P-450$_{c21}$), or the enzyme involved in glucocorticoid synthesis, 11$\beta$-hydroxylase (P-450$_{c11\beta}$), were expressed in the tumor, but they were completely absent in zona glomerulosa of the adjacent adrenal. These findings were consistent with the patterns of primary aldosteronism. Serum potassium level was gradually decreased with concomitant increase in PAC. These results suggest that severe postoperative hyperkalemia of the present case was attributable

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to severe suppression of aldosterone synthesis in the adjacent and contralateral adrenal, which resulted in slow recovery of aldosterone secretion. It is plausible that aldosterone synthesis of adjacent and contralateral adrenal glands is severely impaired in some cases with primary aldosteronism, as glucocorticoid synthesis in Cushing syndrome. ——— aldosteronism; hyperkalemia; postoperative; hypoaldosteronism; paradoxical hyperplasia 

It has been known that some of the patients with aldosterone-producing adenoma show hyperkalemia postoperatively (Gill 1995). This is considered to be due to hypoaldosteronism: inability of the adrenal gland to secrete sufficient amounts of aldosterone immediately after the tumor removal (Kaplan 1994; Gill 1995). It is analogous to the slowness of the return of cortisol production after prolonged ACTH suppression by exogenous glucocorticoids (Kaplan 1994). The aldosterone deficiency is, however, usually neither severe nor prolonged (Kaplan 1994; Gill 1995), and replacement therapy with mineralocorticoid is rarely necessary (Biglieri et al. 1966). Here we report a case of primary aldosteronism, who showed severe hyperkalemia after the removal of an aldosterone-producing adenoma, requiring treatment with cation-exchange resin as well as mineralocorticoid replacement.

## Case Report

A 46-year-old woman was treated under the diagnosis of hypertension since 1994. However, hypokalemia (2.7 mEq/liter) was found and she was referred and admitted to our division for further examinations in August 1997. The patient had past history of unilateral ovarectomy with hysterctomy, resulting in amenorrhea since then. She had paresthesia of the both hands, but no episode of paralysis. Her blood pressure was 170/98 mmHg. Serum sodium and chloride levels were normal (146 mEq/liter and 105 mEq/liter, respectively). Renal function was normal: serum creatinine (0.5 mg/100 ml) and BUN (10 mg/100 ml) levels, and creatinine clearance (89 ml/minutes) were within normal range, and urinary glucose and protein were negative. The endocrinological examinations are shown in Table 1. Plasma renin activity (PRA) was undetectable ($<0.15$ ng/ml/hour, normal range 0.5–2.0 ng/ml/hour) and plasma aldosterone concentration (PAC) was high (370 pg/ml, normal range 56.9–150.0 pg/ml). Other hormone levels were normal, such as cortisol, ACTH or urinary 17-OHCS and 17-KS. Rapid ACTH test was performed with $^{1\text{-}24}$ACTH (0.25 mg, bolus iv) (Koshiyama et al. 1994), which resulted in an increase in both cortisol and PAC (maximum cortisol 219 ng/ml and PAC 833 pg/ml; their normal responses are the peak higher than 200 pg/ml and the increment more than 500 pg/ml, respectively). Both cortisol and PAC showed circadian rhythm. Overnight 1 mg dexamethasone test caused a decrease in both cortisol (11 ng/ml) and aldosterone (157 pg/ml). Posture test was performed as follows: supine posture for 30 minutes, sitting

TABLE 1. *Endocrinological data before the operation*

| Hormone | Value | Unit | Normal range |
|---|---|---|---|
| PRA | <0.15 | ng/ml/hour | (0.5-2.0) |
| PAC | 370 | pg/ml | (56.9-150.0) |
| ACTH | 17.0 | pg/ml | (4.4-48.0) |
| Cortisol | 80 | ng/ml | (27-155) |
| TSH | 2.3 | $\mu$U/ml | (0.4-5.0) |
| fT4 | 14 | pg/ml | (8-23) |
| T3 | 1.37 | ng/ml | (0.80-1.80) |
| Progesterone | <0.1 | ng/ml | (<1) |
| 18-OHDOC | 0.07 | ng/ml | (0.01-0.07) |
| Urinary | | | |
| 17-KS | 5.8 | mg/day | (1.0-8.0) |
| 17-OHCS | 4.4 | mg/day | (2.6-7.8) |

PRA, Plasma renin activity; PAC, Plasma aldosterone concentration; ACTH, Adrenocorticotropic hormone; TSH, Thyroid-stimulating hormone; fT4, free thyroxine; T3, triiodothyronine; 18-OHDOC, 18-hydroxy-11-deoxycorticosterone; 17-KS, 17-ketosteroids; 17-OHCS, 17-hydroxycortiosteroids.

position for 30 minutes, upright standing posture for 60 minutes, and thereafter moderate walking around for 60 minutes. It resulted in an increase in PAC (from 434 to peak level 573 pg/ml), whereas PRA remained undetectable. Ultrasonography, computed tomography, and adrenal scintigraphy showed right adrenal tumor. Venous sampling was performed, which revealed an increase in PAC (3290 pg/ml) in right adrenal vein compared to that in the contralateral adrenal vein (PAC 1280 pg/ml). These findings indicate a diagnosis of right aldosterone-producing adenoma. Spironolactone (75 mg/day) was administered to control hypokalemia for seven days until the operation, which resulted in normal serum potassium level (4.2 mEq/liter). The right adrenalectomy was performed on October 3, which revealed an adrenocortical tumor of 2 cm diameter.

As shown in Fig. 1, ten days after the operation, serum potassium level was markedly increased (up to 6.3 mEq/liter), whereas serum sodium and chloride levels were normal (138 and 103 mEq/liter, respectively). Urinary sodium and postassium excretion was 32 and 228 mEq/day, respectively. Sodium intake (7 g/day) or renal function was not different from those of preoperative period. Pseudohyperkalemia, such as that due to hemolysis, thrombocytosis or leucocytosis, or acidosis were excluded. To treat hyperkalemia, admisnistration of polystyrene sulfonate was started. However, hyperkalemia was persistent and the supplement therapy with mineralocorticoid, i.e., fludrocortsione acetate (up to 0.2 mg/day) was also needed. Basal cortisol and PAC, which were measured 14 days after the operation before any drug administration, were normal (134 ng/ml) and low (39.7 pg/ml), respectively. PRA became detectable (0.41 ng/ml/hour)

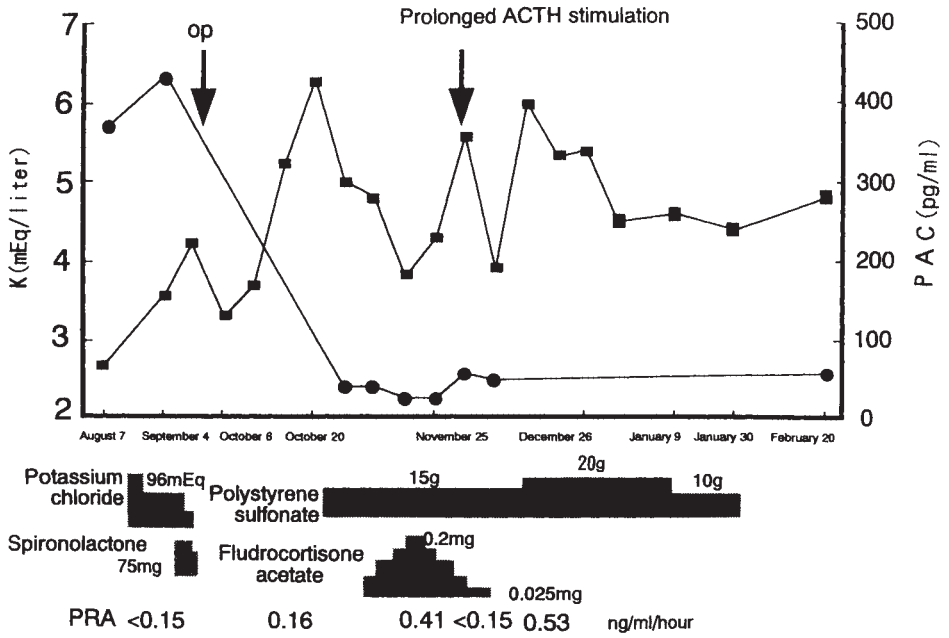
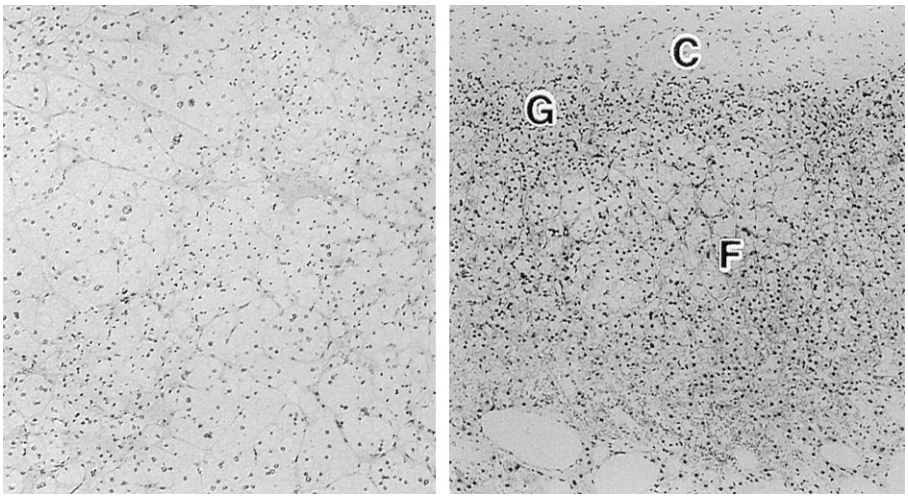



Fig. 1. Clinical course of the patient. ■, serum potassium level (K); ●, Plasma aldosterone concentration (PAC).

one month after the operation, but returned to undetectable range again. Rapid ACTH stimulation test and prolonged ACTH stimulation test ($^{1\text{-}24}$ACTH-Z 0.5 mg/day for 3 days) were performed (Koshiyama et al. 1994). Rapid ACTH test before prolonged ACTH stimulation caused an increase in both cortisol (75 to 195 ng/ml) and PAC (43.9 to 94.3 pg/ml). Prolonged ACTH stimulation test caused an increase in both serum cortisol (475 ng/ml) and urinary 17-OHCS (24.5 mg/day), and a marginal increase in PAC (49.2 pg/ml). Furthermore, after prolonged ACTH stimulation, serum potassium level was transiently decreased, but it was increased again. Gradually PAC increased (57.4 pg/ml and 62.3 pg/ml on November 18 and February 25, respectively) with concomitant decrease in serum potassium level. Administration of polystyrene sulfonate became unnecessary in January 1998 (3.5 months after the operation).

## Materials and Methods

Tissue specimens were sectioned 4 mm thick immediately after excision, fixed in 10% formalin for 36 hours at 4°C and subsequently paraffin-embedded. A small portion of the specimens was fixed in 2.5% glutaraldehyde in phosphate buffer (pH 7.4) and then transferred to 1% osmium tetroxide for postfixation, as described previously (Sasano et al. 1996). Adrenal tumor and adjacent adrenal were examined by light microscopy with immunohistochemistry as previously described (Sasano et al. 1988a, b, 1989a, b, 1990, 1995). Briefly, specific antibodies against the steroidogenic enzymes, including cholesterol side chain cleavage (P-450$_{scc}$), 21-hydroxylase (P-450$_{c21}$), 11$\beta$-hydroxylase (P-450$_{c11\beta}$), 3$\beta$-hydroxysteroid dehydrogenase (3$\beta$-HSD), 17$\alpha$-hydroxylase (P-450$_{c17\alpha}$), and dehydroepiandrosterone sulfotransferase (DHEA-ST) were used. The bitoin-strept avidin




a b

Fig. 2. a, Light microscopic features of the tumor (hematoxylin eosin stain ×200). b, Light microscopic features of the non-neoplastic attached adrenal (hematoxylin eosin stain ×200). *C*, capsule; *G*, the zona glomerulosa; *F*, the zone fasciculata.

(B-SA) amplified method using the Histofine Kit (Nichirei Co., Ltd., Tokyo) was used. Normal rabbit IgG or phosphate buffer at pH 7.4 was used instead of primary antibodies for negative control, and no specific immunoreactivity was detected in these tissue sections.

## Results

The histological examination indicated that the tumor was composed of both large and small clear cells (Fig. 2. left). There were no evidence of adrenocortical malignancy based on the criteria of Weiss (1984). Adjacent non-neoplastic adrenal demonstrated hyperplasia of the zona glomerulosa but zona fasciculata-reticularis were unremarkable (Fig. 2. right). Hypertensive changes including hyalinization of tunica media were present in the arteries in the adipose tissue adjacent to adrenal tumors. Immunohistochemical study of steroidogenic enzymes revealed that tumor cells expressed all the enzymes except for DHEA-ST, including P-$450_{c17\alpha}$ which is required for glucocorticoid biosynthesis but not for mineralocorticoid biosynthesis (Figs. 3a and b). All the enzymes were expressed in the zona fasciculata-reticularis of the attached adrenal including DHEA-ST but hyperplastic zona glomerulosa did not express any of the enzymes examined (Fig. 3c), except for sporadic cortical cells expressing P-$450_{c21}$. Electron microscopic examination revealed relatively abundant mitochondria with lamellar and/or vesicular cristae and smooth endoplasmic reticulum in the tumor cells (Fig. 4).

## Discussion

Postoperative hyperkalemia due to hypoaldosteronism in aldosterone-

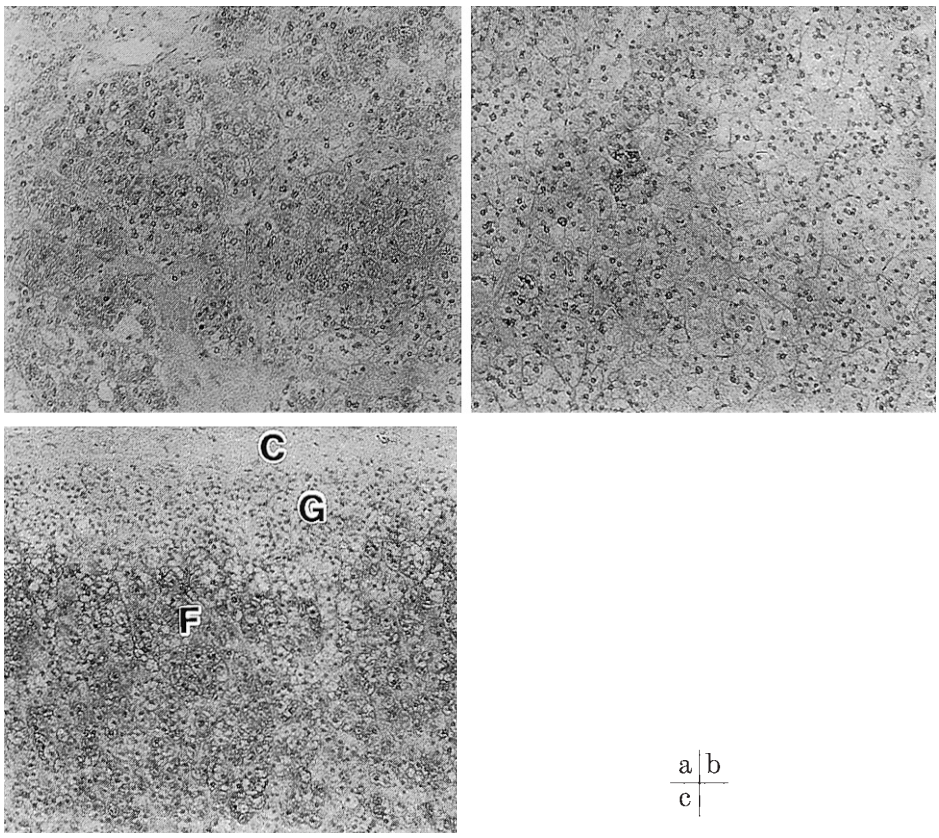



Fig. 3. Immunohistochemistry of 3$\beta$-HSD in tumor ($\times$200).
Immunohistochemistry of P-450$_{c17\alpha}$ in tumor ($\times$200).
Immunohistochemistry of 3$\beta$-HSD in non-neoplastic adrenal ($\times$200).
*C*, capsule; *G*, the zona glomerulosa; *F*, the zone fasciculata.

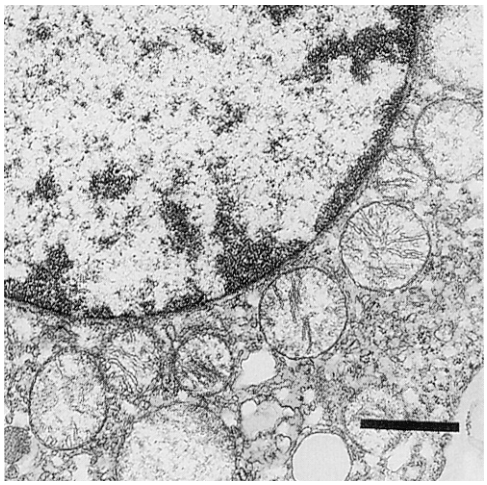


Fig. 4. Ultrastrucural features of the tumor cells. Bar represents 1 $\mu$m.

producing adenoma has been considered to be transient (Kaplan 1994; Gill 1995). In the present case postoperative hyperkalemia was severe, requiring not only cation-exchange resin but also mineralocorticoid supplement. After the operation, basal ACTH was normal and rapid ACTH stimulation test showed an increase in both cortisol and PAC, excluding a state of adrenal insufficiency (Koshiyama et al. 1994; Koshiyama 1996).

The zona glomerulosa of the attached adrenal of primary aldosteronism is expected to show atrophy, as in the zona fasciculata-reticularis of the attached adrenal of Cushing's syndrome, because renin-angiotensin system is markedly suppressed and aldosterone secretion from non-neoplastic adrenal is also markedly diminished. However, it is well known that the zona glomerulosa of the attached non-neoplastic adrenal of primary aldosteronism paradoxically shows "hyperplasia". This has been termed as "paradoxical hyperplasia" (Lack 1997). Immunohistochemistry indicated that the enzymes related to aldosterone synthesis, such as 3$\beta$-HSD and P-450$_{c21}$, and the enzyme involved in glucocorticoid synthesis, P-450$_{c11\beta}$, were positively stained in the tumor, whereas they were completely absent in the zona glomerulosa of the adjacent adrenal. The zona glomerulosa of the attached non-neoplastic adrenal of primary aldosteronism has been demonstrated not to express steroidogenic enzymes involved in aldosterone biosynthesis (Sasano et al. 1988a, b, 1989a, b, 1990, 1995), as in this case. These results suggest that mineralocorticoid production was completely suppressed in the ipsilateral non-neoplastic adrenal gland. Furthermore, the tumor cells expressed P-450$_{c17}$ and contained the mitochondria with vesicular cristae, which are usually detected in outer fasciculata cells, suggestive of neoplastic glucocorticoid production. However, the zona fasciculata and zona reticularis did not show any cortical atrophy, and the expression of DHEA-ST, which is the most ACTH-dependent enzyme in the zona fasciculata and zona reticularis (Sasano et al. 1995), was preserved in the adjacent adrenal. These findings suggested that the amount of neoplastic glucocorticoid production and secretion did not affect hypothalamo-pituitary-adrenal axis of the patient. It can be postulated that the contralateral adrenal gland was in similar condition to that of the adjacent adrenal. The contralateral aldosteorne level (1280 pg/ml) was rather high (normal range of adrenal venous aldosteone levels: 30–90 pg/ml under the same conditon), probably because of non-specific stress caused by the sampling procedure (corisol was also increased in the contralateral adrenal vein). Therefore, although the mineralocorticoid production of both adjacent and contralateral adrenal tissues may have been inhibited, resulting in severe postoperative hyperkalemia, but it could not be concluded that contralateral mineralocorticoid was totally suppressed. These findings are analogous to the suppression of cortisol secretion from the normal adrenal gland after prolonged exogenous glucocorticoids (Kaplan 1994) or after tumor removal in Cushing's syndrome (Biglieri et al. 1966). However, our hypothesis is limited by the fact that neither postural test, low-dose ACTH test nor corticotropin-releasing hormone test was done after the operation. Furthermore, postoperative mineralocorticoid replacement might have confounding effects on the results with rapid and prolonged ACTH tests.

It remains to be elucidated why the present case showed slow recovery of mineralocorticoid synthesis after the operation. Preoperative administration of spironolactone, which may restore the responsiveness of the chronically suppressed

renin-angiotensin-aldosterone axis (Stern and Tuck 1994), failed to prevent the occurrence of postoperative hypoaldosteronism, as earlier reported (Bravo et al. 1975). Biglieri et al. (1966) indicated that hypoaldosteronism recovered within the first month after the operation in most of aldosterone-producing adenoma. However, in some cases, hypoaldosteronism persisted for seven and half months: Two of them required mineralocorticoid replacement (Biglieri et al. 1966). Gordon et al. (1989) reported that PAC returned to "normal levels" as early as 3 months after the operation, which were, however, lower than in the controls 24 months after the operation. Taken together, it is plausible that the mineralocorticoid synthesis of non-neoplastic adrenal tissue is severely impaired in some cases with aldosterone-producing adenoma such as ours, which results in prolonged postoperative hyperkalemia. Mineralocorticoid replacement should be limited to short-term use as possible, since exogenous mineralocorticoid administration may further aggravate slow recovery of contralateral adrenal to synthesize mineralocorticoid.

In summary we reported a case of aldosterone-producing adenoma associated with severe postoperative hyperkalemia, which was attributable to suppression of aldosterone synthesis in the non-neoplastic adrenal, resulting in slow recovery of adrenal to secrete aldosterone. It is suggested that aldosterone synthesis of adjacent and contralateral adrenal glands is severely impaired in some cases with primary aldosteronism, as glucocorticoid synthesis in Cushing's syndrome.

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