A case of primary aldosteronism with secondary hyperparathyroidism and bilateral adrenal tumors

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Summary

A 43-year-old Japanese woman was admitted to our hospital with weakness. Laboratory findings showed hypokalemia, hypocalcemia and elevation of the serum creatinine phosphokinase levels, but intact parathyroid hormone levels. Further evaluations suggested that she had primary aldosteronism (PA), secondary hyperparathyroidism and bilateral adrenal tumors. She was treated successfully by laparoscopic right adrenalectomy. This case not only serves to the diagnosis of bilateral adrenal tumors in which selective adrenal venous sampling (SAVS) proved to be useful, but also for physicians to be aware of secondary hyperparathyroidism and the risk of secondary osteoporosis caused by PA.

Learning points:

- The classic presenting signs of PA are hypertension and hypokalemia.
- Hypokalemia can induce rhabdomyolysis.
- PA causes secondary hyperparathyroidism.
- Patients with PA have the risk of osteoporosis with secondary hyperparathyroidism.
- SAVS is useful in bilateral adrenal tumors.

Background

Primary aldosteronism (PA) represents a cause of secondary arterial hypertension and electrolyte imbalances. PA is typically associated with electrolyte imbalances such as hypokalemia. Hypokalemia can also induce rhabdomyolysis. In recent decades, dynamic studies have demonstrated multiple biological properties of aldosterone on calcium metabolism. We herein report the case of PA with secondary hyperparathyroidism and bilateral adrenal tumors.

Case presentation

A 43-year-old Japanese woman had a history of hypertension for 5 years and had been on treatment with

antihypertensive agents, including amlodipine and candesartan. She noticed recurrent episodes of limb muscle weakness during the previous 2 years. She was admitted to our hospital with severe weakness. Physical examination on admission revealed a blood pressure of 155/89 mmHg, pulse rate of 81/min, and severe flaccid weakness of the proximal muscles of all four limbs, with relative sparing of the distal groups and tenderness in the lower extremities.

Investigation

Laboratory findings showed severe hypokalemia (1.8 mEq/l) and extreme elevation of the serum creatinine phosphokinase (CPK) levels (6929 IU/l). Based on the previous findings, the patient was diagnosed as having

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Figure 1

Abdominal computed tomography (CT) showed a low-density right adrenal mass measuring 23 mm in diameter and a left adrenal mass measuring 15 mm in diameter.

hypokalemic quadriplegia and rhabdomyolysis. Furthermore, laboratory findings showed lower total serum calcium corrected for albumin (corrected calcium) level (8.0 mg/dl), elevation of intact parathyroid hormone (PTH) levels (126.2 pg/ml) and secondary hyperparathyroidism. Because the secondary hyperparathyroidism was related to the high-turnover bone disease, we assessed the bone turnover markers. Tartrate-resistant acid phosphatase 5b (TRACP5b) as bone resorption marker was 247 mU/dl (normal range 120–420 mU/dl), whereas procollagen type I N-terminal propeptide (PINP) as bone formation marker was 32.4 µg/l (normal range 17.1–64.7 µg/l). The lumbar bone mineral density (BMD) was 110% of the young adult mean (YAM) and the femoral neck BMD was 85% of YAM. Osteopenia or osteoporosis was not present.

Treatment was initiated by oral and intravenous supplementation of potassium, which was followed within two weeks by resolution of the symptoms and return of the serum CPK levels to normal, without the development of any renal complication. Two weeks after stopping amlodipine and candesartan, further evaluation revealed extremely high aldosterone-renin ratio (ARR) (more than 3083 pg/ml per ng/ml per h) and elevated urinary aldosterone excretion (70.1 µg/day). Abdominal computed tomography (CT) showed a low-density right adrenal mass measuring 23 mm in diameter and left adrenal mass measuring 15 mm in diameter (Fig. 1). Serum cortisol showed the typical circadian rhythm. Serum cortisol was sufficiently suppressed with a 1 mg overnight dexamethasone suppression test. The level of ARR was still high after the captopril test (more than 200 pg/ml per ng/ml per h). Plasma renin activity (PRA) remained suppressed (0.2 ng/ml per h) after stimulation with furosemide (40 mg) plus upright posture for 60 min when hypotensive episodes occurred. ¹³¹I-aldosterol scintigraphy showed increased uptake of the tracer in the right adrenal gland (Fig. 2).

Subsequently, the plasma aldosterone concentration (PAC) and plasma cortisol levels in adrenal venous effluents obtained by selective adrenal venous sampling (SAVS) before and after ACTH (Cortrosyn: 250 µg) stimulation are shown Table 1. Basal aldosterone levels in the right and left adrenal vein were 28 000.0 pg/ml and 484.7 pg/ml, respectively, which rose to 31 000.0 pg/ml and 3081.8 pg/ml, respectively, 20 min after ACTH stimulation. The aldosterone concentrations in the right adrenal vein were greater than 2500 pg/ml before ACTH stimulation and greater than 14 000.0 pg/ml 20 min after ACTH stimulation, which suggested unilateral hypersecretion of aldosterone from the right adrenal gland. Based on the cortisol levels in the right and the left adrenal veins after ACTH stimulation (970.0 and 344.0 µg/dl; more than 200 µg/dl), we considered that the catheters had been correctly inserted into the adrenal vein. We also took into account the ratio of aldosterone/cortisol (A/C) on the right side to that on the left side after ACTH stimulation (the A/C ratio), which was 3.6 (>2.6). The data obtained from SAVS strongly suggested preferential aldosterone hypersecretion from the right adrenal gland. All these results strongly suggest the presence of prominent excess of aldosterone from the right adrenal gland in this case.

Treatment

The patient was treated successfully by laparoscopic right adrenalectomy. The histology of the resected specimen was consistent with functioning adrenal adenoma. Immunohistochemical analysis of 3β-hydroxysteroid dehydrogenase (3β-HSD) showed positive immunoreactivity in cortical cells of the nodules (Fig. 3a) and hyperplastic zona glomerulosa cells (Fig. 3b).

Figure 2

¹³¹I-aldosterol scintigraphy showed increased uptake of the tracer in the right adrenal gland.

Table 1 Selective adrenal venous sampling.

	Inferior vena cava	Right adrenal vein	Left adrenal vein
Before ACTH stimulation			
PAC (pg/ml)	556.9	28 000.0	484.7
Cortisol (μg/dl)	13.3	36.4	28.7
A/C	41.9	769.2	16.9
After ACTH stimulation			
PAC (pg/ml)	1080.0	31 000.0	3081.8
Cortisol (μg/dl)	20.1	970.0	344.0
A/C	53.7	32.0	9.0

Outcome and follow-up

After the operation, the patient's symptoms improved, the PAC and PRA reverted to normal and the serum potassium levels also returned to and remained normal. PTH and fractional excretion of calcium (FECa) decreased, whereas corrected calcium elevated. Furthermore, TRACP5b as a bone resorption marker decreased, whereas PINP as bone formation marker increased (Table 2). There was no recurrence 1 year after the operation. However, the contra-lateral adrenal mass should be followed up morphologically and functionally.

Discussion

We present here a case of PA with secondary hyperparathyroidism and bilateral adrenal tumors. The mechanism of secondary hyperparathyroidism with PA is as follows. Hyperaldosterone leads to hypercalciuria and hypocalcemia which cause secondary hyperparathyroidism. The hypercalciuria associated with aldosteronism is thought to be related to an expansion of extravascular fluid volume with resultant reductions in proximal tubular Na^+ and Ca^{2+} resorption. This leads to their increased delivery to distal segments of the nephron, where the mineralocorticoid promotes Na^+ resorption without affecting Ca^{2+} which results in hypercalciuria (1). Furthermore, accumulating clinical evidence suggests a bidirectional interplay between PTH and aldosterone (2). In particular, hyperaldosteronism is reported to elevate urinary calcium excretion (3). Pilz *et al.* (4) reported in ten PA patients lower serum calcium and higher plasma PTH levels compared to essential hypertension (EH) patients. Maniero *et al.* (5) showed a highly significant 31% increase in the number of cases of hyperparathyroidism. Ceccoli *et al.* (6) in 116 PA patients compared with 110 EH patients showed urinary calcium excretion and an elevation of PTH levels.

In bone metabolism, Pilz *et al.* documented significantly lower BMD in PA patients compared to patients without hyperaldosteronism. The mechanism underlying this association is directly by aldosterone-mineralocorticoid receptors (MR)-mediated effects on osteoblasts and osteoclasts and indirectly by PTH levels and increased bone reabsorption (7). Maniero *et al.* (8) demonstrated the expression of the MR in both PTH secreting adenoma and in parathyroid tissue, and MR was predominantly located in the nucleus of the parathyroid cells. Finally, Tomaschitz *et al.* (2) showed that patients with PA were with secondary hyperparathyroidism that could be successfully treated with either mineral corticoid receptor antagonists or adrenal surgery.

Our patient showed hypersecretion of aldosterone from the right adrenal gland because of the greater PAC in the right adrenal vein after ACTH stimulation and ^{131}I -adosterol scintigraphy showed increased uptake of the tracer in the right adrenal gland. The histology of the resected specimen was functioning adrenal adenoma. Immunohistochemical analysis of 3β -HSD showed positive immunoreactivity in cortical cells of the nodules and hyperplastic zona glomerulosa cells. These data show not only the cortical cells of micronodules actively synthesize aldosterone, but also what the hyperplastic zona glomerulosa cells might do. Nishimoto *et al.* (9) demonstrated that immunohistochemistry of the human normal adrenal cortex for Aldosterone synthase (CYP11B2) may provide a pathological confirmatory diagnosis of adrenocortical adenomas, but we cannot investigate the immunohistochemistry of CYP11B2. In bone metabolism, lower corrected calcium level, elevation of PTH level and secondary hyperparathyroidism could be successfully treated with adrenal surgery.

Our patient was also diagnosed as rhabdomyolysis. Rhabdomyolysis is a disorder characterized by acute damage of the skeletal muscle and caused by various conditions such as muscle diseases, intense exercise,

Figure 3

(a) The cortical cells of the nodules (N) showed positive immunostaining for 3β -HSD ($\times 10$). (b) Hyperplastic zona glomerulosa (ZG) cells also showed positive immunostaining for 3β -HSD ($\times 10$).

Table 2 Postoperative course.

	Preoperative	Postoperative
PRA (ng/ml per h)	0.2	2.1
PAC (pg/ml)	616.5	140.5
PAC/PRA	3082.5	66.9
Intact-PTH (pg/ml)	126.2	37.3
Corrected Ca (mg/dl)	8.0	8.8
P (mg/dl)	2.6	3.3
FE _{Ca} (%)	1.1	0.5
TRACP5b (mU/dl)	247	164
PINP (μg/l)	32.4	45.4
BMD lumbar (%YAM)	110	106
Femoral (%YAM)	85	82

dehydration, various drugs such as statins, infections, poisoning and hypokalemia. Hypokalemia may potentially cause rhabdomyolysis by three mechanisms. First, increased blood flow to the anaerobic muscle is mediated by release of intracellular potassium into the extravascular spaces. With hypokalemia, release of potassium may be inadequate to vasodilate arterioles and capillaries that perfuse the exercising muscle. Second, hypokalemia has been shown to suppress the synthesis and storage of glycogen, an intracellular store of energy substrate for the exercising muscle. Finally, deranged ion transport across the cell membrane has been demonstrated (10).

In conclusion, this case provides an important lesson that further investigation of the cause of hypokalemia must be pursued. The present case also serves to the diagnosis of bilateral adrenal tumors in which SAVS proved to be a useful diagnostic tool for its localization. However, a long-term follow-up is needed to observe whether or not aldosterone hypersecretion may occur from the left adrenal gland tumor. Furthermore, the present case serves to underscore the need for physicians to be aware of secondary hyperparathyroidism and the risk of secondary osteoporosis caused by PA.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The authors confirm that written informed consent was obtained from the patient for publication of the submitted article and accompanying images through his signature on their consent form.

Author contribution statement

Dr S Miyauchi attended to the patient and contributed to the writing of this case report.

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