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Case Report

A case of primary aldosteronism combined with acquired nephrogenic diabetes insipidus

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ABSTRACT

Aldosterone-producing adrenal adenoma can induce various clinical manifestations as a result of chronic exposure to aldosterone. We report a rare case of a 37-year-old man who complained of general weakness and polyuria. He was diagnosed with aldosterone-producing adrenal adenoma and nephrogenic diabetes insipidus. Aldosterone enhances the secretion of potassium in the collecting duct, which can lead to hypokalemia. By contrast, nephrogenic diabetes insipidus, which manifests as polyuria and polydipsia, can occur in several clinical conditions such as acquired tubular disease and those attributed to toxins and congenital causes. Among them, hypokalemia can also damage tubular structures in response to vasopressin. The patient's urine output was >3 L/d and was diluted. Owing to the ineffectiveness of vasopressin, we eventually made a diagnosis of nephrogenic diabetes insipidus. Laparoscopic adrenalectomy and intraoperative kidney biopsy were subsequently performed. The pathologic finding of kidney biopsy revealed a decrease in aquaporin-2 on immunohistochemical stain.

Introduction

Primary aldosteronism is characterized by hypertension, hypokalemia, and sodium retention resulting from chronic oversecretion of aldosterone. In most cases, primary aldosteronism is due to a unilateral adrenal adenoma (65–75%), an idiopathic bilateral adrenal hyperplasia (33%), or—in rare cases—an adrenal carcinoma or aldosterone-producing ovarian cancer [1]. These cases typically present with symptoms of muscle weakness, paralysis, polyuria, headache, and sensory disturbances. Most patients had hypertension, but some had also had tetany and paralysis. The clinical symptoms associated with hypokalemia include muscle weakness, paralysis, rhabdomyolysis, arrhythmia, impaired urinary concentration, and hyperglycemia [1]. Therefore, most patients with primary aldosteronism are admitted to hospitals for headaches related to hypertension or symptoms associated with hypokalemia [1].

We report a rare case of a patient with primary aldosteronism who presented with hypokalemia and diabetes insipidus (DI). Interestingly, this patient was found to have a water channel aquaporin-2 (*AQP2*) deficiency during the immunohistochemical examination of the kidney. We also reviewed several reports of primary aldosteronism associated with either hypokalemia or acquired nephrogenic DI.

Case report

A 37-year-old man with a history of hypertension was admitted to the emergency department for symptoms of muscle weakness and paralysis. He had been diagnosed with hypertension at 28 years of age. His blood pressure had been

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well controlled with calcium channel blockers for 10 years. He had been suffering from muscle weakness and paralysis for several years.

On examination, his blood pressure was 150/90 mmHg and his heart rate was 64 beats/min. His laboratory blood chemistry results revealed a low potassium level, Na 147 mmol/L, K 1.91 mmol/L, Cl 108 mmol/L, and total CO_2 27.8 mmol/L. However, calcium (8.7 mg/dL), magnesium (2.2 mg/dL), and phosphorus (3.8 mg/dL) were within normal levels. The arterial blood gas analysis showed the following values—pH 7.435, P_{CO_2} 46.5 mmHg, P_{O_2} 87.7 mmHg, HCO_3^- 30.5 mmol/L, O_2 saturation 97.1%—which indicated metabolic alkalosis. Other studies included BUN/creatinine level of 11/0.7 mg/dL, and the urinary chemistry profile showed a high potassium level of 18.56 mmol/L, a low urine osmolality of 199 mOsm/kg, and a transtubular potassium concentration gradient of 20. On the 2nd day of hospitalization, the collected 24-hour urine test revealed the following values: creatinine 317 mmol/d, urea nitrogen 2,834 mg/d, sodium 322 mmol/d, potassium 88 mmol/d, calcium 379 mg/d; moreover, proteinuria was not detected. The patient's thyroid hormone level was within normal limits. His plasma aldosterone (PA) level was 224.7 pg/dL and the plasma renin activity (PRA) was as low as 0.11 ng/mL, resulting in a high PA/PRA ratio. Even though a saline loading test showed an intermediate aldosterone level (7.68 ng/dL), a left adrenal mass measuring 2 cm was observed in abdominal computed tomography (CT; Fig. 1).

Although the patient had not noticed any polyuria, his urinary volume was >3 L/d during his admission. His antidiuretic hormone (ADH) level rose (224.7 pg/mL). His brain magnetic resonance imaging result showed a normal pituitary gland, and he had an insignificant response to the water deprivation test after stimulation by vasopressin injection. This ruled out central DI and suggested nephrogenic DI. The patient received potassium infusions, and his potassium level improved from 1.91 mmol/L to 3.86 mmol/L. Subsequently, the patient was placed on 50 mg spironolactone daily.

Finally, a laparoscopic-assisted left adrenalectomy was performed, and the corresponding biopsy revealed it to be an adenoma (Fig. 2). We also needed to prove that aldosteronism, hypokalemia, and DI occurred sequentially. According to Marples et al [2], prolonged hypokalemia resulted in the downregulation of AQP-2 expression in a rat kidney. However, this has not been demonstrated in humans; therefore, a renal biopsy was also performed during the laparoscopy to investigate potential renal pathology.

There were approximately 46 glomeruli, eight of which were completely sclerotic. Many of the remaining glomeruli showed elongated cigar-shaped capillary loops with mesangiolysis. There were no segments of sclerosis, adhesion, or crescents. Capillary walls and basement membranes were thickened but singly contoured. Many proximal tubules were flattened with a loss of brush borders and were detached from the tubular basement membranes. The others had markedly swollen cytoplasm, resulting in luminal narrowing, in which brush borders were well preserved. The interstitium was markedly edematous and infiltrated by lymphocytes. In terms of water channels in the kidney, the immunohistochemistry showed that AQP-2 expression was significantly decreased, but that of other AQP channels, AQP-1 or AQP-3, was not different compared to that in a healthy kidney (Fig. 3). On the 3rd day after surgery, the serum potassium level normalized to 4.5 mmol/L without replacement of potassium, the PA level decreased to 26.7 pg/dL, and PRA increased to 0.37 ng/mL, resulting in a lower PA/PRA ratio. Urine output also decreased to <2 L/d, and the patient was discharged from the hospital.

Discussion

This is a rare case where acquired nephrogenic DI associated with chronic hypokalemia was caused by an aldosterone-secreting adrenal adenoma.

Primary aldosteronism refers to conditions in which the production of aldosterone, a steroid hormone produced in the adrenal gland, is inappropriately high. Such overproduction of aldosterone causes cardiovascular damage, hypertension, sodium retention, and potassium excretion that, if prolonged and severe, may lead to significant potassium deficiency [1]. Hypokalemia is one of the most important symptoms of primary aldosteronism. The mechanism of hypokalemia is usually explained by accelerated potassium excretion into renal distal tubules in response to aldosterone excess. The arterial hypertension of primary hyperaldosteronism is explained by an increase in sodium reabsorption related to

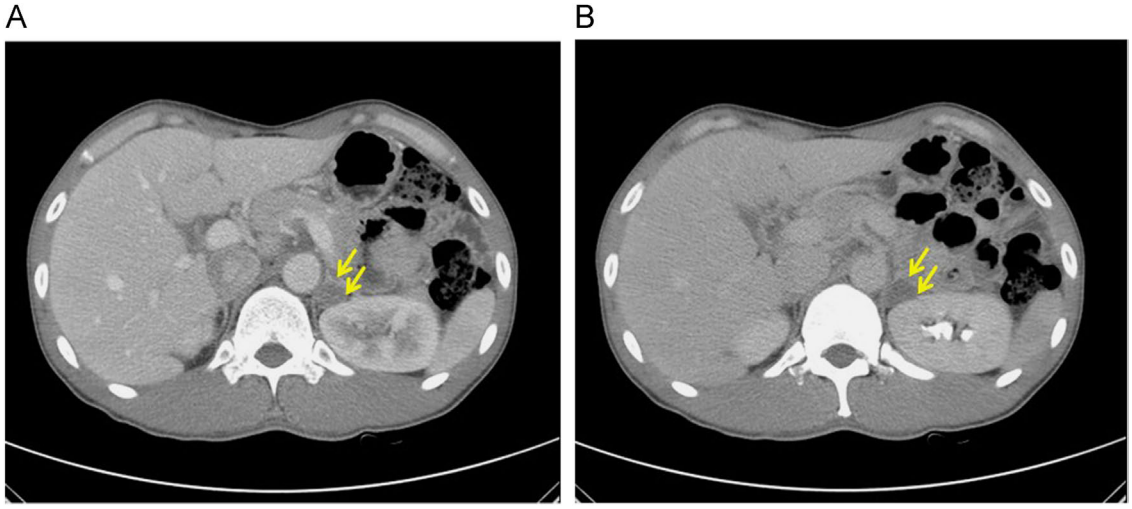

Figure 1. Abdominal computed tomography (CT). (A) An approximately 2-cm mass lesion is noted at the left adrenal gland, which has a low density on precontrast CT. (B) No definite enhancement was observed on dynamic CT image. This is a small adrenal mass lesion (benign rather than malignant).

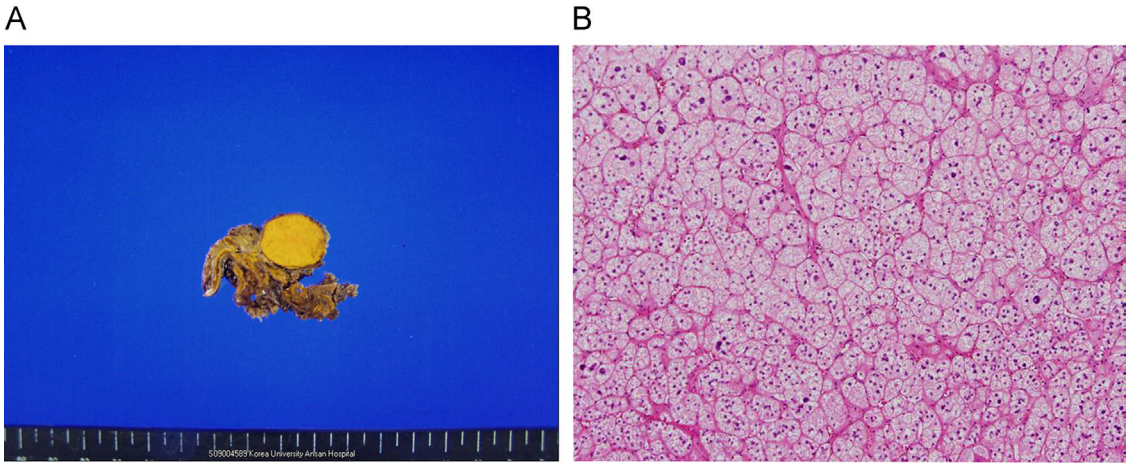

Figure 2. Adrenal biopsy findings from a patient with primary aldosteronism. (A) The specimen of an enlarged adrenal gland, measuring 5.7 cm × 3.2 cm × 1.8 cm, shows its external surface with a focally polypoid appearance. The cut surface shows a relatively well-capsulated diffuse bright yellowish solid mass, measuring 2.0 cm × 1.7 cm across. (B) Adrenal biopsy shows cells uniform in size and shape that resemble mature cortical cells. Occasionally, there is some nuclear and cellular pleomorphism but with no evidence of anaplasia. They have uniform nuclei and well-differentiated, abundant cytoplasm (producing cholesterol-rich materials such as hormones).

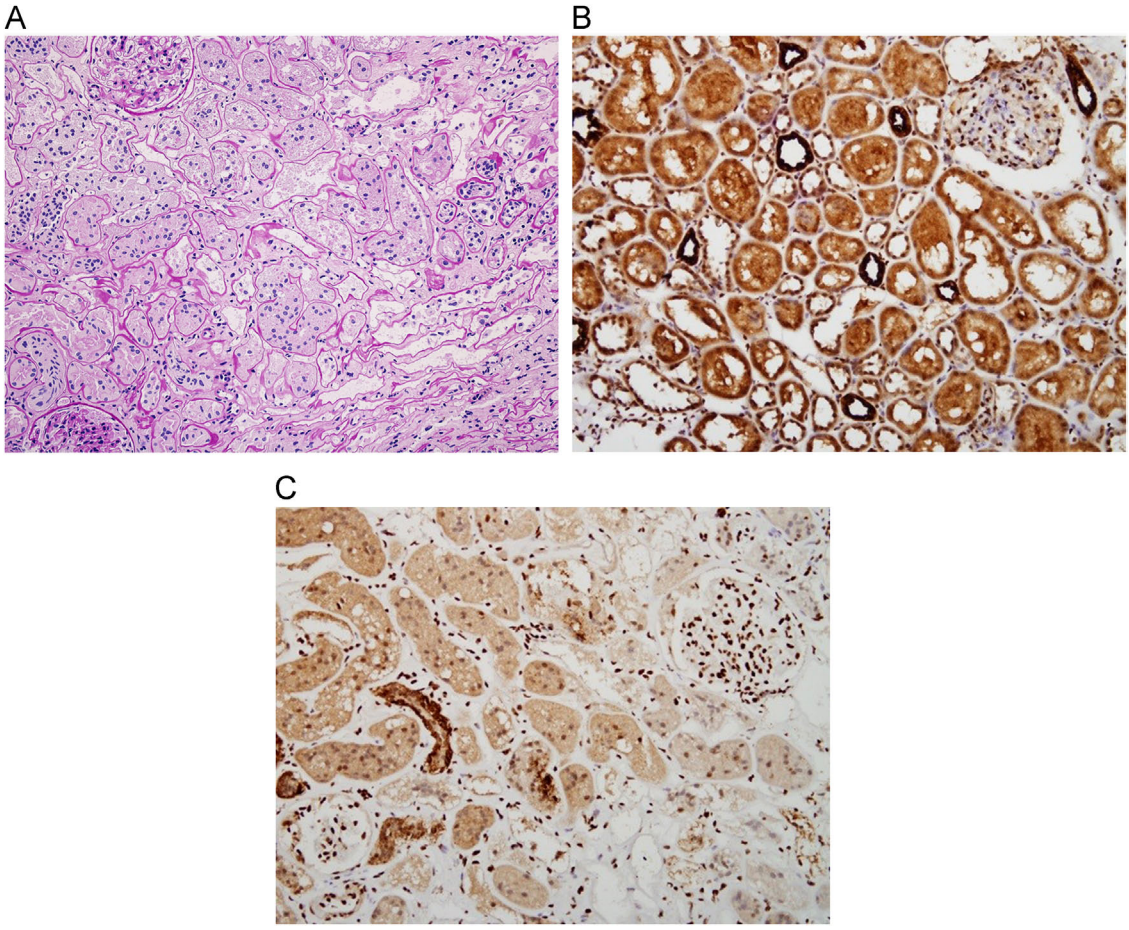

Figure 3. Renal biopsy findings from a patient with primary aldosteronism. (A) The biopsy specimen for conventional light microscopy shows no segments of sclerosis, adhesion, or crescents. Other structures such as capillary walls and basement membranes, tubules, and cytoplasm are preserved or mildly changed. However, there is a patchy area of chronic inflammatory changes such as glomerular sclerosis, tubular atrophy, and associated interstitial fibrosis (periodic acid-Schiff stain, × 200). (B) The normal kidney biopsy from control person using immunohistochemistry for aquaporin-2 (AQP-2) shows normal expression (× 200). (C) The patient's renal biopsy reveals decreased AQP-2 expression, compared to that in a normal kidney using immunohistochemistry (× 200).

the effect of aldosterone on distal renal tubules. This transient hypervolemia, along with the direct effects of aldosterone, induces secretion of natriuretic factors such as atrial natriuretic peptides [3]. Blood pressure remains high owing to several factors, including increased peripheral vascular resistance, a direct hypertensive effect of aldosterone on the

central nervous system, and increased vascular sensitivity to pressor substances such as angiotensin and adrenalin. However, the clinical and biological spectrum of primary aldosteronism varies [3]. In particular, hypokalemia is present in 7–38% of patients with primary aldosteronism, ranging from 1.4 mmol/L to 3.5 mmol/L. In most cases, younger patients were diagnosed by high blood pressure and neuromuscular signs and symptoms associated with hypokalemia.

Primary aldosteronism is commonly caused by benign tumors of the adrenal gland, overactivity of steroid-producing cells in the adrenal cortex, or—in rare cases—hereditary conditions or adrenal cancer [1]. PRA can be measured as a screen for primary aldosteronism. Although members of the general population have PRA levels < 1.0–2.0 ng/mL/h, 25% of patients with essential hypertensive show decreased PRA and increased aldosterone levels [1]. To differentiate these diseases, the PA/PRA ratio should be examined. Primary aldosteronism is possible if the ratio exceeds 30. It is strongly suggested when the ratio is > 50.

An adrenal CT scan should be examined to classify the subtype, identify the location, and rule out adrenal cortical carcinoma [1]. In the case of an aldosterone-secreting adenoma, a unilateral adrenal adenoma was reported that measured 1.8 cm on average and < 1 cm in 19% of patients. Primary aldosteronism usually occurs from an adenoma or a bilateral hyperplasia. Adrenal adenoma is generally treated with surgery via a unilateral approach, whereas bilateral hyperplasia is treated with medical therapy. However, there are limitations to diagnosing adrenal adenomas with CT, because it is still difficult to discover the location between the right and left sides, and even more difficult to diagnose bilateral hyperplasia. Therefore, adrenal venous sampling might be the most accurate and definitive diagnosis tool for small adenomas and bilateral hyperplasia. However, in the case of highly suspicious aldosterone-secreting adenomas, if the mass is well defined, hypodense, and > 1 cm on CT scan, then laparoscopic adrenalectomy can be considered, and adrenal venous sampling can be bypassed [1].

By contrast, acquired nephrogenic DI results from a decreased expression of AQP-2, which leads to impairment of urinary concentration. AQP-2 (water channel proteins) are located in the principal cells of the collecting duct, and they regulate water permeability. When ADH binds to type 2 vasopressin receptor on the basolateral membrane of the principal cell, AQP-2 are carried by cytoplasmic vesicles and then distributed into the apical membrane. Water in the apical membrane enters through AQP-2 and exits into the basolateral membrane through AQP-3 and -4 [4]. Hypokalemia seems to cause a reduction in the intracellular level of cAMP, which acts as the second messenger for ADH. It then leads to the downregulation of AQP-2. This mechanism is similar to that of lithium-induced nephrogenic DI; however, hypokalemia-induced DI is believed to have a relatively modest effect compared with lithium, and complete recovery is possible when hypokalemia is corrected [2].

Hyperaldosteronism most commonly occurs from secondary causes and can result in severe complications. Several cases complicated with secondary hypertension by adrenal adenoma have been reported in Korea: aortic dissection, one of severe left ventricular septal hypertrophy, basal ganglia intracranial hemorrhage, and two cases of preeclampsia [5–8]. Moreover, hypokalemia due to hyperaldosteronism has been reported in several case studies with periodic paralysis, two cases of rhabdomyolysis, and one instance of cardiac arrest during adrenalectomy [9–11]. A case of nephrocalcinosis and renal cyst was reported related to hypokalemia [12].

Chronic hypokalemia leading to acquired nephrogenic DI was reported in a patient with renal artery stenosis in Korea [13]. Furthermore, several cases of renal disease related to hypokalemic nephrogenic DI, without confirmed hyperaldosteronism, have been reported in patients with multiple autoimmune syndrome and multiple myeloma [14,15]. Interestingly, in our case, renal biopsy showed evidence of chronic renal tubulointerstitial injury and decreased expression of AQP-2 in the renal collecting tubules.

In summary, the authors confirmed an adrenal adenoma in a patient with hypertension and hypokalemia using CT for investigation of the potential causes of primary aldosteronism. Moreover, chronic renal tubulointerstitial injury and AQP-2 deficiency developed because of chronic hypokalemia associated with primary aldosteronism.

Conflict of interest

None.

Acknowledgments

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