CASE REPORT

Primary Aldosteronism Caused by Unilateral Adrenal Hyperplasia: Rethinking the Accuracy of Imaging Studies

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A rare type of aldosteronism, known as unilateral adrenal hyperplasia (UAH), is difficult to diagnose, not only because it fails to conform to the typical common subtypes, but also because imaging results are unreliable. We report 2 Taiwanese patients with UAH. Case 1 was a 44-year-old man with 2 episodes of hypokalemic paralysis. Hypertension and suppressed plasma renin activity (PRA) with elevated plasma aldosterone concentration (PAC) were observed. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) showed a right adrenal mass, but adrenal scintigraphy revealed no definite laterality. The patient underwent a laparoscopic right adrenalectomy. Adrenal cortical hyperplasia was discovered from results of the histologic analysis. Case 2 was a 33-year-old woman referred for hypokalemia, hypertension, and a left adrenal mass found on a CT scan. However, MRI revealed normal adrenal glands. The adrenal vein sampling for PAC showed overproduction of PAC from the left adrenal gland. A laparoscopic left adrenalectomy was done. Pathology results revealed micronodular cortical hyperplasia with central hemorrhage. Blood pressure, plasma potassium, aldosterone, and renin activity levels returned to normal after operation in both cases. Both patients have been well for 3 years and 16 months, respectively, after surgery. We review the literature and discuss the limitations of imaging studies. [*J Chin Med Assoc* 2006;69(3):125–129]

Key Words: aldosterone, aldosteronism, renin activity, unilateral adrenal hyperplasia

Introduction

Primary hyperaldosteronism is characterized by hypertension, hypokalemia, elevated plasma aldosterone levels, and suppressed plasma renin activity (PRA). The 2 main classical types of the disorder are aldosterone-producing adenoma (APA) (best treated surgically) and idiopathic hyperaldosteronism (IHA) (best treated medically).[1] Unilateral adrenal hyperplasia (UAH) is an uncommon variant of primary aldosteronism. There have been only a few case reports of unilateral adrenal hyperplasia since this disorder was proposed by Ross in 1965.[2] Clinical and biochemical presentations can be similar to an aldosterone-producing tumor, and the final diagnosis can only be made postoperatively by pathologic examination. We describe 2 Taiwanese patients with unilateral adrenal hyperplasia and discuss the limitations of imaging studies.

Case Report

Case 1

This 44-year-old man was discovered to have hypokalemia in 1996 when an episode of muscle weakness brought him to the emergency department. Six years before the current episode, he was found to have hypertension during an extracorporeal shock wave lithotripsy (ESWL) procedure, but he paid little attention to this.

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At that time, his blood pressure (BP) was 174/108 mmHg. He was found to have a serum potassium level of 1.9 mEq/L. The plasma aldosterone concentration (PAC) and PRA were noted to be 134 pg/mL (normal, 37~240) and 0.1 ng/mL/h (normal, 0.15~2.33), respectively. A computed tomography (CT) scan performed on 5-mm slices of the adrenal glands showed a hypodense nodule in the lateral limb of the right adrenal gland (Table 1). After discharge, the patient was lost to follow-up until another episode of muscle weakness developed 3 years later. His BP was 201/101 mmHg. Serum chemistry revealed levels of sodium 143 mEq/L, potassium 1.54 mEq/L, and increased muscle enzymes (creatine kinase, 855 IU/L and myoglobulin, 403 μg/L). After potassium replacement, the upright serum aldosterone level and PRA were examined. Because of the high serum aldosterone (360 pg/mL) and suppressed PRA (0.4 ng/mL/h) associated with hypertension and hypokalemia, serial examinations were performed. A physical examination showed an obese man with a BP of 160/90 mmHg but otherwise unremarkable. The family history was noncontributory to hypertension.

The PAC did not fall (187→219 pg/mL) after captopril provocation. Aldosterone and cortisol measurements at 08:00 after overnight recumbency were 148 pg/mL and 7.7 μg/dL, respectively; aldosterone increased to 376 pg/mL and cortisol to 18.5 μg/dL after 4 hours of ambulation. However, the PRA did not increase after ambulation (0.4→0.2 ng/mL/h). Blood chemistry showed impaired fasting blood glucose (120 mg/dL). Arterial gas analysis revealed metabolic alkalosis with a base excess of +8.6 mmol/L.

The results of CT of 3-mm slices of the adrenal gland were similar to those performed 3 years previously (Figure 1A). However, an adrenal scintigram using ^{131}I-6-β-iodomethyl-19-norcholesterol (NP-59) with dexamethasone suppression showed no definite abnormal uptake in the bilateral suprarenal regions up to day 7 after the injection. Magnetic resonance imaging (MRI) presented a well-defined right adrenal nodular lesion measuring approximately 10 mm in diameter with chemical shift imaging (Figure 1B).

A laparoscopic right adrenalectomy was performed. The pathology showed macronodular hyperplasia (Figures 2A and 2B). Postoperatively, the patient's BP reduced to a normal range, and his serum potassium level normalized. Three years after surgery, his upright 2-hour PAC was 127 pg/mL and PRA was 1.1 ng/mL/h. He has remained normotensive and normokalemic. His fasting plasma glucose was 105 mg/dL.

Table 1. Lateralization data of study patients

	CT	MRI	AVS	NP-59	Lateralization	Clinical response
Case 1	Right nodule	Right nodule	NA	Normal	Right	Yes
Case 2	Left nodule	Normal	Left	NA	Left	Yes

AVS = adrenal venous sampling; CT = computed tomography scan; MRI = magnetic resonance imaging; NA = not available; NP-59 = ^{131}I-6-β-iodomethyl-19-norcholesterol scan.

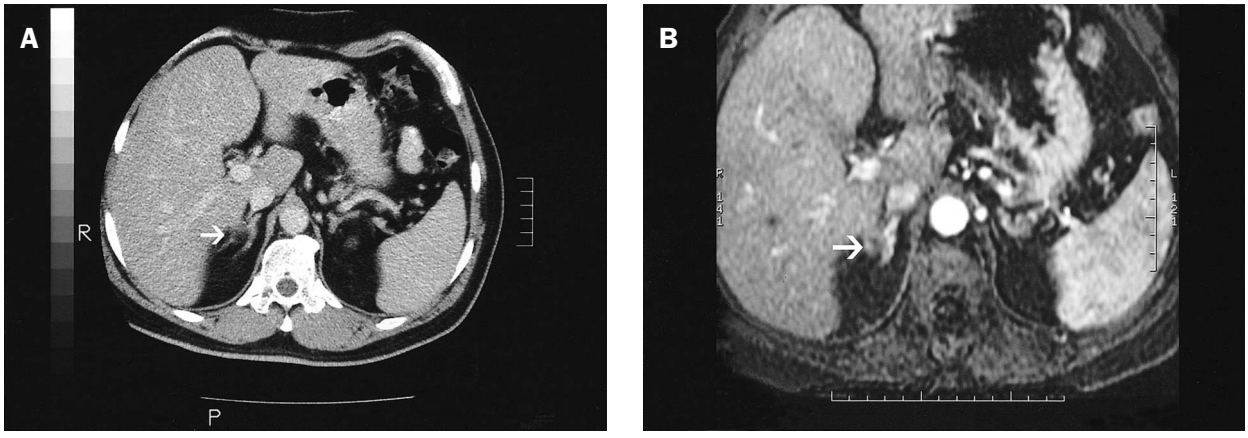

Figure 1. Abdominal computed tomography (CT) scan (A) and magnetic resonance image (MRI) (B) of case 1. (A) A CT scan showing a hypodense nodule in the lateral limb of the right adrenal gland (arrow). (B) MRI presenting a well-defined right adrenal nodular lesion 10 mm in diameter (arrow).

Case 2

A 33-year-old female nurse was referred to our urologic department because CT had revealed a left adrenal mass. She had experienced episodic bouts of frontal headaches, nausea, and visual disturbances for 1 year. An elevated BP of 180/110 mmHg and hypokalemia of 3.2 mEq/L were found. A physical examination revealed an obese woman with BP of 150/110 mmHg. The association of hypertension, hypokalemia, and an adrenal tumor suggested a diagnosis of Conn's syndrome, but MRI showed no definite nodular lesion or focal enlargement in either adrenal gland. To further clarify the laterality, selective adrenal-venous sampling (AVS) for determination of PAC and cortisol levels was performed. PAC and cortisol levels in the left adrenal vein were markedly elevated, to 915 pg/mL and 82 μg/dL, respectively. However, PAC and cortisol levels in the right adrenal vein were 90 pg/mL and 21.2 μg/dL, respectively. PAC levels at other sites, such as the right adrenal vein and inferior vena cava, were equivalent to those in the peripheral veins. PRA was less than 1.0 ng/mL/h at all sites.

The patient suffered from left abdominal pain after AVS. The imaging study showed a left adrenal hematoma. The patient underwent a left laparoscopic adrenalectomy 3 days later. The resected mass, weighing 25 g, was diagnosed pathologically as micronodular cortical hyperplasia with central hemorrhage (Figure 2C).

Follow-up of the patient for 16 months after the adrenalectomy showed her to be in good health. She has had only occasional headaches. Her supine PAC was 137 pg/mL, PRA was 1.9 ng/mL/h, and serum potassium was 5.1 mEq/L. The patient's BP at home and at the office continued to remain in a normal state for 16 months with no medication.

Discussion

Primary aldosteronism is the principal disorder of the zona glomerulosa. Some subsets, including APAs, IHA, and inherited entities, have been identified. Primary UAH and aldosterone-producing renin-responsive adenomas (APRAs) are variants of primary aldosteronism.

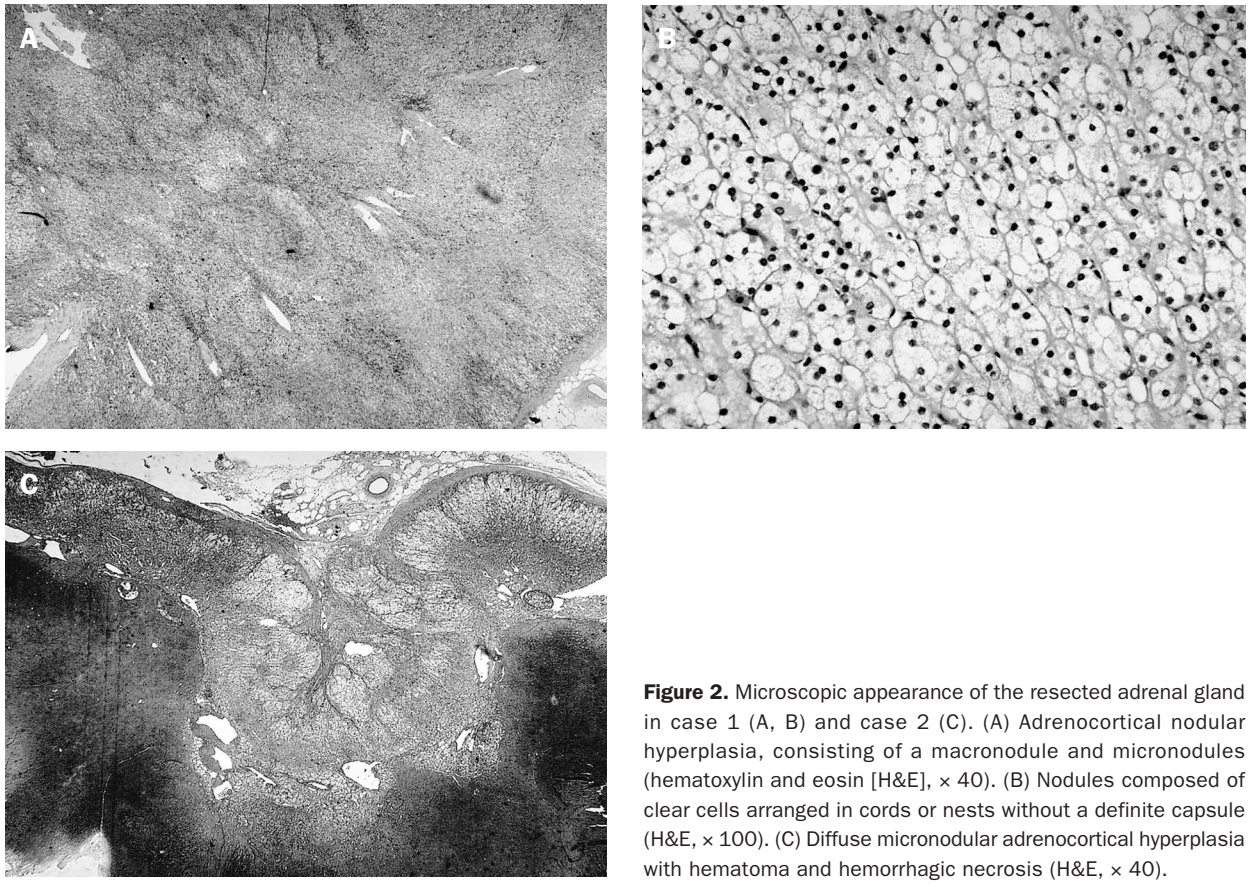

Figure 2. Microscopic appearance of the resected adrenal gland in case 1 (A, B) and case 2 (C). (A) Adrenocortical nodular hyperplasia, consisting of a macronodule and micronodules (hematoxylin and eosin [H&E], × 40). (B) Nodules composed of clear cells arranged in cords or nests without a definite capsule (H&E, × 100). (C) Diffuse micronodular adrenocortical hyperplasia with hematoma and hemorrhagic necrosis (H&E, × 40).

We present 2 unusual cases of primary aldosteronism. They had evidence of unilateral adrenal disease but were found to have micronodular or macronodular hyperplasia. Further studies, which were performed several months later, revealed that the hyperaldosteronism and suppressed PRA were no longer present. In patients with hyperaldosteronism due to bilateral adrenal hyperplasia, PRA usually remains low after a unilateral adrenalectomy.[1] Persistent hypertension is common in patients with bilateral adrenal hyperplasia even after a total adrenalectomy.[1] Our patients became normotensive after the operation and remained so throughout the period of follow-up. These findings suggest that primary aldosteronism in these patients resulted from overproduction of aldosterone solely from the resected adrenal.

The possibility that UAH can cause primary aldosteronism was suggested by Ross in 1965.[2] Ganguly et al[3] reported a patient with a more definitive response to surgical removal of unilateral hyperplastic adrenal gland diagnosed by AVS. Subsequently, there have been intermittent case reports of unilateral cortical hyperplasia causing primary aldosteronism.[4–13] A diagnosis of this type of aldosteronism is usually made retrospectively when AVS reveals the unilateral aldosterone source but a hyperplastic adrenal cortex is discovered after an operation. UAH should also be presumed, even though histology reveals hyperplasia, and the BP and aldosteronism become normal after surgery. However, there are variable degrees of improvement in the hypertension after the operation.[3–13] Data on long-term benefits are limited.

The pathogenesis of UAH is not clearly understood. This disorder is thought to be a precursor of adenoma formation or an intermediate state between APA and IHA.[4] In our patient 1, however, his nodular lesion on CT scan remained unchanged after 3 years. This disorder may have a different pathogenesis. Banks et al[14] first characterized primary adrenal hyperplasia (PAH) in 1984 as hyperplastic adrenal glands that resemble IHA morphologically but mimic the APA response to ambulation and to surgical removal of 75% of both adrenal glands. Whether UAH and PAH are the same disease remains to be determined. UAH is also sometimes termed PAH.[8,10]

A number of methods have been used to localize the source of the hyperaldosteronemia. There is continuing debate about the optimal method of evaluating patients with proven primary aldosteronism for determining the subtype. For instance, an increase in the plasma aldosterone level with ambulation is occasionally seen in patients with adrenal adenoma, presumably due to stress-related or incidental episodic secretion of adrenocorticotropic hormone. Hormonal characteristics of UAH have been reviewed,[4] and the basal PAC level and its responses for differentiating APA from IHA have been verified.

As a cause of primary aldosteronism, UAH is a rare subset, and only 30 cases have been reported. Thirty-two cases, including the present 2 cases, with some examples providing inadequately documented data, were reviewed (Table 2). The data show the limitations of imaging studies and scintigraphy for evaluating patients with UAH. The adrenal imaging studies (CT or MRI) demonstrated unilateral nodular lesions and a normal contralateral gland in 10 of 24

Table 2. Imaging and scintigraphic features of reported cases with unilateral adrenal hyperplasia[2-13]

	Total tested, *n*	Results	Number affected
CT or MRI	24	Affected side nodule	10
		Affected side plumpness	4
		Bilateral nodule	1
		Bilateral plumpness	1
		Normal	6
		Unaffected side nodule	1
		Unaffected side plumpness	1
NP-59	13	Affected side uptake	3
		Early affected side uptake	3
		Bilateral uptake	6
		Unaffected side uptake	1

CT = computed tomography scan; MRI = magnetic resonance imaging; NP-59 = ^{131}I-6-β-iodomethyl-19-norcholesterol scan.

patients. Another 4 patients had incongruent results in comparison with AVS. The adrenal glands appeared normal on CT images in 6 patients. Four patients had unilateral adrenal enlargement. Adrenal scanning with or without dexamethasone was performed in 13 cases. In 6 of these cases, a bilateral uptake pattern was observed; in 3 cases, the affected adrenal was correctly identified; and, in 3 cases, early uptake was seen on the correct side, although bilateral uptake was seen on day 5.

Detection of laterality in patients with UAH is difficult by scintigraphy alone. The sensitivity of isotope scanning depends on the size of the aldosterone-producing area.[15] CT and/or MRI also raise their own problems. An asymmetrically enlarged hyperplastic gland or a gland with macronodular/micronodular hyperplasia has the potential to be misinterpreted. Also, the incidence of "adrenal incidentalomas" can make the interpretation of a lesion even more fraught with difficulty. Many clinicians rely on CT and MRI to distinguish between unilateral and bilateral disease, citing the technical difficulties and risks of AVS. AVS was initially described in the 1960s. Determining the laterality of aldosterone secretion by this method has an accuracy of 95%.[1] The aldosterone ratio between the left and right adrenals should be greater than 5:1 if a true unilateral source of aldosterone is present.[8,10] In most cases of APA, the ratio is greater than 10:1.[10] This technique fell into disfavor because of the difficulty of cannulating both adrenal veins and a small but significant risk of venous thrombosis, adrenal hemorrhage, or adrenal insufficiency.

UAH may, however, be more common than believed, as it is likely that some patients are being treated medically. These results indicate that CT and/or MRI imaging is unreliable for diagnosing UAH. If excessive reliance is placed on CT and MRI scans without adrenal sampling, serious errors may be made.

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