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CASE REPORT

A patient with concurrent primary aldosteronism and Page kidney

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Abstract The ratio of aldosterone-to-renin activity is currently recommended as a screening test for primary aldosteronism (PA). There are many factors interfering the interpretation of aldosterone–renin ratio (ARR) and could hamper in-time diagnosis of PA. Here, we first report a patient with underlying Page phenomenon and an accidentally disclosed adrenal incidentaloma. High renin secretion from Page phenomenon had masked higher ARR into normal ARR obscuring the diagnosis of PA. However, adrenal venous sampling (AVS) confirmed the autonomous aldosterone secretion with left adrenal vein plasma aldosterone concentration (PAC) 124.1 ng/dl and a lateralization ratio 3.3. AVS may discriminate masked PA due to high renin secretion from Page kidney. It is suggested that clinicians should cautiously interpret aldosterone–renin ratio and consider diagnostic AVS if hyperaldosteronism is highly suspected especially in the background of other secondary hypertension.

Keywords Primary aldosteronism · Aldosterone–renin ratio · Page kidney · Adrenal venous sampling

Abbreviations

ACE	Angiotensin converting enzyme
ARR	Aldosterone–renin ratio
APA	Aldosterone-producing adenomas
AVS	Adrenal venous sampling
CT	Computerized tomography
PAC	Plasma aldosterone concentration
DRC	Direct renin concentration
VMA	Vanillylmandelic acid
ACTH	Adreno-cortico-tropic-hormone

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NP-59-SPECT/CT	I-^{131}-6-beta-iodomethyl-norcholesterol single-photon emission computed tomography/ computed tomography
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Introduction

Primary aldosteronism (PA), characterized by hypertension, hypokalemia, low renin status and unsuppressed aldosterone secretion from the adrenal glands, has been increasingly recognized after the ratio of aldosterone-to-renin (ARR) has been adopted as the first-line screening tool [1, 2]. Besides, in recent published data, the overall prevalence of PA has reached 11.2% among newly diagnosed hypertensive patients in referred tertiary centers and has turned to be the most prevalent secondary hypertension [1, 3]. However, the application of ARR is not without false positive and false negative rate, especially in patients receiving sympatholytic drugs such as β adrenergic blockers or clonidine, due to suppression of renin, and in those who taking diuretics or angiotensin-converting enzyme inhibitors (ACEIs) from the stimulation of renin [3]. Besides, the coincidentally existed other etiologies of secondary hypertension would also interfere the interpretation of ARR and thus hampered the diagnosis of PA [4]. In the presenting case, we first describe a patient with underlying Page phenomenon from previously subcapsular hemorrhagic cystic lesion whose unsuppressed renin lead to insufficient ARR to facilitate the diagnosis of PA. Adrenal venous sampling (AVS) eventually confirmed excessive autonomous aldosterone secretion from left adrenal incidentoloma. To our knowledge, there is no report of coexisting Page phenomenon and PA in the current literatures. It is proper to conduct AVS in patients with an adrenal tumor and a known other cause of secondary hypertension despite the low ARR.

Case report

In February 2006, a previously healthy 38-year-old man presented to the hospital for a 1-week course of right flank pain. He was a non-smoker and had medical history of 2-year hypertension (stage 1) and chronic gout. On presentation, the blood pressure was 150/90 mmHg but his blood pressure was consistently elevated to 190/110 mmHg on the following measurements in spite of anti-hypertensive medication use (nifedipine 30 mg bid). Laboratory tests showed creatinine 1.1 mg/dl (normal 0.6–1.3) and serum potassium 4.7 mmol/l (normal 3.5–5.2). Chest X-ray revealed left ventricular hypertrophy but there was no retinopathy. Studies for secondary hypertension were all negative including 24-h urine VMA (5.17 mg/24 h, normal 1–7), cortisol (11.5 μg/ml, normal 5–20 at 8 a.m.), and ACTH(11.8 pg/ml, normal 9–52). However, abdominal enhanced computed tomography (CT) scan showed a right renal subcapsular hematoma, suggested a peri-renal hemorrhagic cyst, measuring 9.0 × 6.5 cm which compressed the renal parenchyma (Fig. 1). In contrast, renal artery stenosis (RAS) was not detected on abdominal magnetic resonance imaging. The adrenal glands were intact on both abdominal CT and MR studies. Since the persistently elevated blood pressure, Page kidney phenomenon was considered and we tried to aspirate the hemorrhagic cyst via a pig-tail catheter transcutaneously but in vain. The hypertension was then managed medically and the flank pain gradually subsided. One year later, persistent hypertension in this age and blood pressure higher than 140/90 mmHg even on three anti-hypertensive medications including calcium channel blockers, alpha blockers, and ACE inhibitors raised the suspicion of PA. Though the screening ARR was high to 84 ng/dl per ng/ml/h (ARR cut-off is >35 in TAIPAI database [2, 5]) and the confirmatory test via captopril suppression unveiled suspicious PA (PAC 12.1 ng/dl), the subtype differentiating test by NP-59 SPECT/CT was negative. Hypertension could be only confidently attributed to Page phenomenon. At his 41-year-old, a fall down accident led to an abdominal CT study which identified an incidental left adrenal tumor (0.9 × 0.8 cm). However, the right previous hemorrhagic cystic lesion has been partially resolved (Fig. 2). Repeat screening ARR (PAC 34.6 ng/dl; PRA 0.13 ng/ml/h, ARR 266.5) was elevated but another confirmatory test for PA, saline-infusion test (SIT), was negative (Table 1). To exclude the possible functional

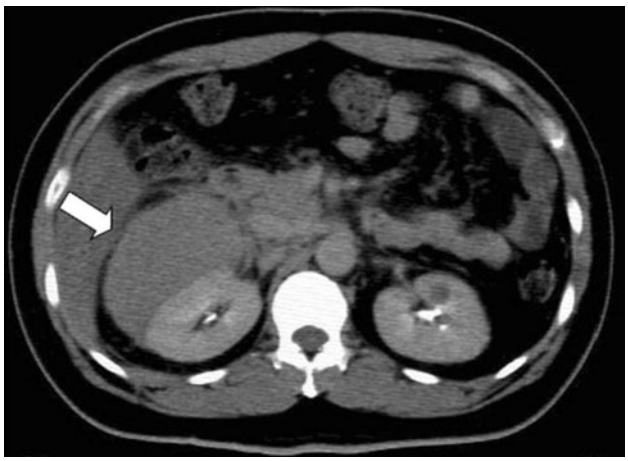

Fig. 1 The abdominal CT scan at patient's 38-year-old revealed a subcapsular hematoma measuring 9.0 × 6.5 cm at the right kidney (*arrow*)

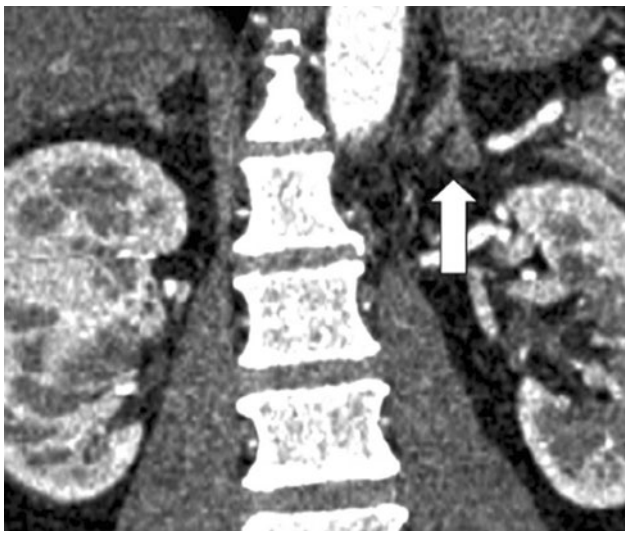

Fig. 2 An adenoma measuring 0.9 × 0.8 cm at the left adrenal gland (*arrow*) was incidentally identified 3 years later

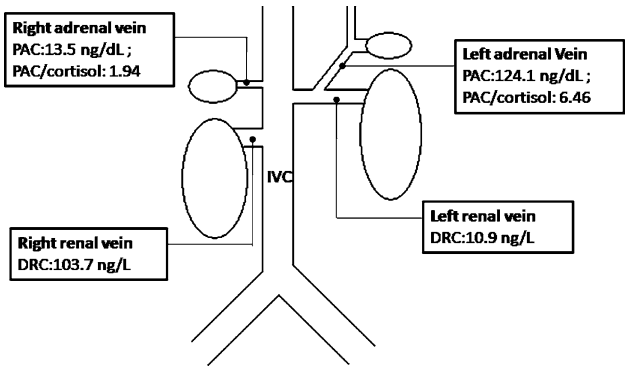

Fig. 3 The results of PAC, DRC, and PAC/cortisol ratio were derived from adrenal venous sampling (AVS). *Numbers in boxes* denoted the levels of PAC, DRC, and PAC/cortisol ratio in each sampling veins. The lateralization index, the left PAC/cortisol ratio divided by right PAC/cortisol ratio, was 3.3 (6.46/1.94) which indicated the left lateralization. Abbreviations: *PAC* plasma aldosterone concentration, *DRC* direct renin concentration, *IVC* inferior vena cava

incidantoloma, AVS was conducted and the aldosterone levels in the left and right adrenal veins were 124.1 and 13.5 ng/dl, respectively, and the ratios of aldosterone/cortisol were 6.46 and 1.94 to left and right sides, respectively. The DRC levels in the right and left renal vein were 103.7 and 10.9 ng/l (Fig. 3). The diagnosis of APA was then ascertained due to the established lateralization (lateralization ratio 3.3). Surgical intervention was suggested but the patient refused. Currently, he is maintained in spironolactone monotherapy with good blood pressure control.

Method: measurement of aldosterone and renin level

The concentration of aldosterone (plasma aldosterone concentration, PAC) was measured by radioimmunoassay (RIA) using commercial kits (Aldosterone MAIA Kit, Biochem ImmunoSystems, Bologna, Italy) [6]. The detection limit was 10.0 ng/l with a 90% confidence interval and the normal range was 35–300 ng/l in an upright position. Plasma renin activity (PRA) was measured as the generation of angiotensin I in vitro using a commercially available RIA kit (Incstar Corporation, Stillwater, Minnesota, US). Its normal range was 2.63 ± 1.32 ng/ml/h in an upright position [6]. The plasma DRC level was measured by immunoradiometric (sandwich technique) assay, using a commercially available kit (Renin III Generation; CIS Bio International, Schering SA, Gif/Yvette, France) according to the manufacturer's instructions [7].

Discussion

ARR is mathematically highly dependent on renin [8]. Thus, concomitant RAS or other renoparenchymal disease such as glomerulonephritis could influence the renin secretion and thereby obscure the underlying disorder [9]. Three cases of PA without suppressed renin have been reported by Oelkers et al. [4]. The escape of renin from suppression due to secondary hypertension-related parenchymal kidney damage often confused the diagnosis of PA while using ARR as the initial screening tool [4]. Drawbacks of ARR could raise the likelihood of misdiagnosis [1]. First, factors including age, serum potassium level, timing and position of sampling collection, and various

Table 1 Sequential change of plasma aldosterone and renin levels

	Initial screening (Jan 2, 2007, 1 year after hemorrhagic cyst)	Captopril suppression test (Jan 31, 2007)	Hypertension clinic follow up, second screening (Mar 17, 2008)	Saline-infusion test (Jul 11, 2008)	Repeat screening before adrenal venous sampling
PAC (ng/dl)	43.7	12.1	34.6	34.5	34.4
PRA (ng/ml/h)	0.52	–	0.13	8.28	3.49 (DRC, ng/dL)
ARR (ng/dl per ng/ml/h)[a]	84	–	266.5	4.17	9.86

PAC plasma aldosterone concentration, *PRA* plasma renin activity, *ARR* aldosterone-to-renin ratio, *DRC* direct renin concentration

[a] ARR cut-off value was 35 ng/dl per ng/ml/h on screening and confirmatory tests in TAIPAI study group [2, 5, 6]

medications affect ARR [1, 10]. Second, low renin status may lead to a false positive ARR results regardless of the PAC [11]. Therefore, the interpretation of ARR should be cautiously made [12].

In our patient, hyperaldosteronism characterized by autonomous aldosterone secretion from the left-sided adrenal tumor was demonstrated only by AVS. The disproportionately high DRC concentration in right renal vein, resulted from previous subcapsular hematoma—the Page phenomenon, could be explained for his normal ARR from unsuppressed renin. The high DRC in the Page phenomenon is provoked by external compression to the renal parenchyma leading to focal ischemic and hypoperfusion which activate the renin–angiotensin–aldosterone system with subsequent high renin and aldosterone status [13]. The improvement in his hypertension after replacing ACE inhibitors to mineralocorticoid receptor antagonist was consistent with the diagnosis of PA.

Regarding the role of AVS, it has been regarded as the most reliable test to differentiate subtypes of PA [14]. In the past, clinicians took conservative attitude toward AVS because the procedure is technically difficult on cannulating the right adrenal vein and is not without risk of adrenal vein rupture [15]. Although the cutoff value of lateralization index (aldosterone/cortisol ratio) varies from centers to centers, a threshold of >3 has been validated in a series of aldosterone-producing adenoma in our hospital [16].

The utility of AVS as initial diagnostic test is "never" mentioned in the current literature. Other ancillary diagnostic tests including cosyntropin testing and intraprocedural adrenal vein and peripheral vein gradient are now seldom used by current guideline [1]. However, in case of the possible concomitant high renin status, above-mentioned diagnostic tests may play important roles to delineate the discrepancy between the right and left adrenal venous aldosterone and renin levels. Besides, immunocytochemistry expressions of corticotrophin (MC2R), angiotensin II type 1 receptor (ATIR), 17α-hydroxylase have been emerged as molecular markers to assist the differential diagnosis of adrenal functionality. In addition, common mutations in germ line aldosterone synthetase gene and hybrid genes in evaluation of adrenal mass lesions also help differentiating the subtype of PA [17]. The elevated DRC of renal cyst may be further differentiated from PA by estimation of 18-hydroxycorticosterone (18-OH-B), 18-hydroxycortisol (18-OH-F), and salivary aldosterone level [18]. Use of cortisol corrected ARR or corticotrophin stimulated ARR during sequential or simultaneous bilateral AVS may also be advantageous. In general, cortisol corrected PAC/cortisol lateralization ratio >4.0 often confirms unilateral aldosterone excess whereas <3.0 suggest bilateral hypersecretion [19]. Adrenal vein/peripheral vein PAC ratio >2.5 (124.1/34.4 = 3.6 in our case) on either side further confirms lateralization. In our patient, lateralization ratio was 3.3 and the presence of adenoma on CT image supported the diagnosis of APA. AVS is therefore indicated as essential for lateralization of PA before surgical intervention, though being invasive, expensive, and requiring special expertise, and thus remains as a highly selective procedure for screening of highly prevalent PA [10–15%] among hypertension subjects.

From the presenting case, AVS is crucial in diagnosis, confirmation, and subtype differentiation of PA. AVS should be considered in patients with other secondary hypertension and an adrenal incidentaloma even though the normal ARR. On the other hand, although the normal range of DRC in renal vein is unknown, higher DRC in right renal vein implies the hyper-secretion of renin from right kidney. The primary physicians must be aware that the ARR in screening or confirmatory tests of PA may obtain false negative results in patients with high renin status.

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