

Case Report

Curable congestive heart failure in patients with primary aldosteronism: two cases reports

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Abstract: Primary aldosteronism (PA) is characterized by overproduction of aldosterone which can lead to various target organ damage, including the cardiovascular system. There are rare case reports about PA patients with severe heart failure. We report two male patients who were admitted because of severe cardiac systolic dysfunction induced by primary aldosteronism. Their cardiac function improved significantly after target therapy. Patient A was a 33 year old male with serum aldosterone concentration (PAC) 251.3 pg/ml, renin activity (PRA) 0.04 ng/ml/h, and aldosterone-to-renin ratio (ARR) 627.5. Computed tomography (CT) revealed a tumor in the left adrenal gland, while no dominant secretion function was found in the left side after the adrenal veins sampling (lateralization index 0.99). Bilateral adrenal hyperplasia was diagnosed and spironolactone was prescribed. Left ventricular ejection fraction (LVEF) was improved from 30% to 45% at the 11-month follow-up visit. Patient B was 43 years old male with PAC 185.5 pg/ml, PRA 0.46 ng/ml/h and ARR 403.2; Captopril challenge test was positive and a microadenoma (2.7*3.2*2.8 cm) was revealed on CT. Unilateral aldosterone-producing adenoma was diagnosed. His LVEF was improved from 30% to 51% at 12 months after laparoscopic adrenalectomy. Thus, it is important to screen for PA in patients with heart failure and launch the appropriate treatment for such patients.

Keywords: Heart failure, primary aldosteronism, targeted therapy

Introduction

Congestive heart failure (CHF) is a leading cause of hospitalization, with a high risk of mortality and re-hospitalization. Identifying the underlying mechanisms including cardiac (myocardial and valvular abnormalities) and noncardiac (toxic damage and metabolic derangements) is crucial to guide the appropriate management to improve outcomes.

Primary aldosteronism (PA) is characterized by aldosterone (ALD) overproduction and plasma renin suppression, which has been the most common cause of hypertension secondary to endocrine disorders [1]. More recently, researchers reported that excessive aldosterone is associated with vascular and perivascular inflammation, fibrosis, and oxidative stress [2], which then increase the risk of cardiovascular

events, including heart failure, atrial fibrillation, myocardial infarction and stroke [3]. It is estimated that there could be more than 12 million PA patients in China [4]. However, there are only few case reports regarding the association between heart failure, especially heart failure with reduced ejection fraction (HFrEF), and PA [5]. Herein, we report two patients with congestive heart failure cured after successful PA management. Patients provided written informed consent to participate in this study.

Case report

Case 1

Patient A, a 33-year-old male without significant past medical history presented with paroxysmal nocturnal dyspnea and exertional dyspnea which had been occurring for two months.



Figure 1. Electrocardiogram of patient 1 (A) and patient 2 (B). Electrocardiogram of Patient 1 (A) showed sinus tachycardia and a flat T wave in leads II, III, and aVF. Electrocardiogram of Patient 2 (B) revealed sinus rhythm, a flat T wave and ST depression in lead I, aVL and V4-6 leads.

His maximum exercise tolerance was only 20 meters of walking. Upon evaluation, heart rate was 122 beats per minute, BP 106/64 mmHg, and weight 80 kg. Per auscultation, there were moist rales over lower lung fields bilaterally. Impulse was palpated 1 cm outside the left midclavicular line and the liver was palpated 3 cm below the right costal margin. Severe pitting edema was noticed over the lower extremities below knees bilaterally.

Labs revealed N-terminal pro-brain natriuretic peptide (NT-proBNP) >30000 pg/ml, serum potassium 4.8 mmol/L, serum sodium 139 mmol/L, serum aldosterone concentration (PAC) 251.3 pg/ml (range 30-160 pg/ml), plas-

ma renin activity (PRA) 0.04 ng/ml/h (range 0.15-2.33 ng/ml/h), and the aldosterone-to-renin ratio (ARR) 627.5 (range <20). Electrocardiogram (ECG) showed sinus tachycardia and a flat T wave in leads II, III, and aVF (**Figure 1A**). Echocardiography suggested the left atrium diameter (LAD) 50 mm, the left ventricle end-diastolic diameter (LVEDD) 68 mm, the right atrium diameter (RAD) 47 mm, the right ventricle diameter (RVD) 32 mm with calculated left ventricular mass index (LVMI) 118.4 g/m², wide pulmonary artery with moderate mitral regurgitation (MR), mild tricuspid regurgitation (TR), and impaired left ventricular ejection fraction (LVEF 30%). Cardiac MRI suggested an enlargement of the entire heart with thinning of the left and right ventricles but without evidence of ventricular wall perfusion abnormality. CT scan revealed a slightly low-density nodule (3.0*2.2 cm) in the left adrenal area (**Figure 2**). Coronary angiography revealed no evidence of coronary artery disease (CAD).

We conducted adrenal venous sampling (AVS), however no dominant difference of al-

dosterone secretion (lateralization index 0.99) was proved, suggesting no dominant secretion function from the left adrenal gland/nodule (**Table 1; Figure 3**) and more likely bilateral adrenal hyperplasia (BAH). Further management with spironolactone 20 mg three times daily was added to his regular HFrEF regimen including metoprolol 25 mg twice daily, trimetazidine 20 mg three times daily, and telmisartan 20 mg once daily.

Eleven months later, he was asymptomatic during his activities of daily living (ADLs). Physical exam revealed body weight of 74 Kg and HR of 80 bpm. Repeat NT-proBNP was 1107 pg/ml. Echocardiogram showed improvement of EF

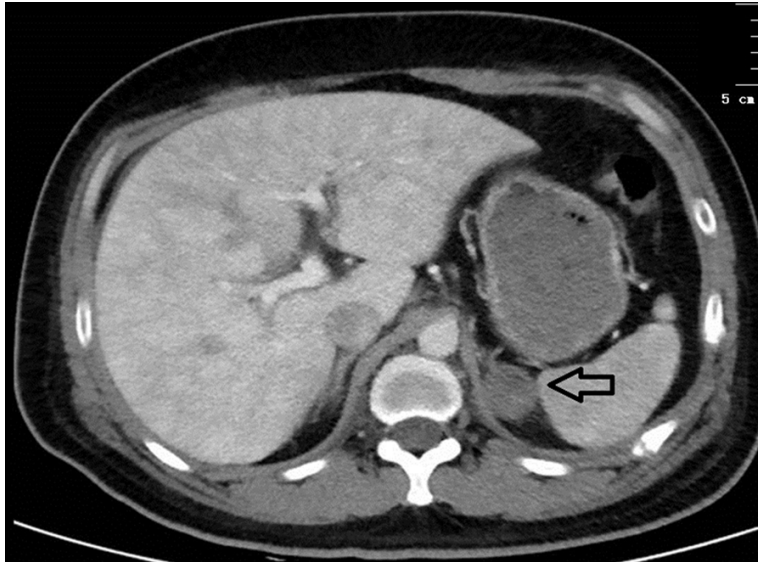


Figure 2. Abdominal computed tomography scan revealed a left adrenal mass (3.0*2.2 cm) (arrow).

Table 1. The results of adrenal venous sampling

	left adrenal vein	right adrenal vein	inferior vena cava
aldosterone (pg/ml)	1533.8	1020.6	160.7
cortisol (ng/ml)	7000.5	4617	218.7
selectivity index	32.0	21.1	
lateralization index	0.99		

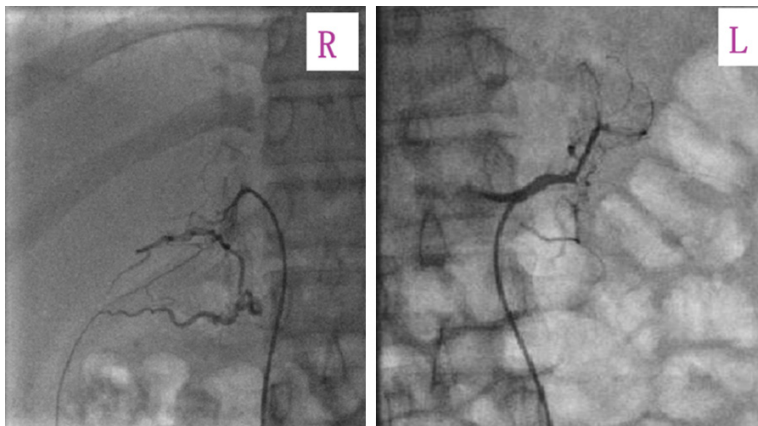


Figure 3. Adrenal venous sampling showed the adrenal vein. Adrenal venography images obtained with right adrenal vein (R) injection showed a delta pattern of veins, while the left adrenal veins (L) were distorted by the tumor and capsular veins spread around it. The catheter was 5Fr (1.65 millimeters).

from 30% to 45% and a significant reduction of heart size (LAD from 50 mm to 30 mm, LVEDD from 68 mm to 58 mm, RAD from 47 mm to 36 mm, and RVD from 32 mm to 20 mm).

Case 2

Patient B, a 43-year-old male with essential hypertension (EH) was admitted for progressive shortness of breath (SOB). His SOB onset was around 1 year ago but worsened with lower extremity edema around 5 days prior to this admission. Physical examination revealed HR of 96 bpm, BP of 142/110 mmHg, moist rales over bases of the lungs bilaterally per auscultation, impulse felt outside the left midclavicular line, and moderate pitting edema of lower extremities.

Labs revealed serum potassium 4.5 mmol/L, serum sodium 141 mmol/L, NT-proBNP 7970 pg/ml, serum troponin 0.021 ng/ml (range 0-0.034 ng/ml), PAC 185.5 pg/ml, PRA 0.46 ng/ml/h, and ARR 403.2. The captopril challenge test showed that the PAC at 8 AM was 192.7 pg/ml with PRA 0.3 ng/ml/h. After taking 50 mg captopril, the PAC increased to 213.2 pg/ml with PRA 0.1 ng/ml/h at 10 AM. ECG revealed sinus rhythm, flat T wave, ST depression in lead I, aVL, and V4-6 leads (**Figure 1B**). Echocardiography suggested impaired LVEF (42%) and heart enlargement with LAD 43 mm, LVEDD 65 mm, RAD 38 mm, and RVD 23 mm. LVMI was 138.6 g/m². Coronary angiography revealed no evidence of coronary abnormalities. There was a nodule found in the left adrenal area (2.7*3.2*2.8 cm) from CT abdomen/pelvis (**Figure 4A**).

This patient was diagnosed with aldosterone-producing adenoma (APA) and bypassed AVS and proceeded directly to surgery. He received laparoscopic adrenalectomy successfully

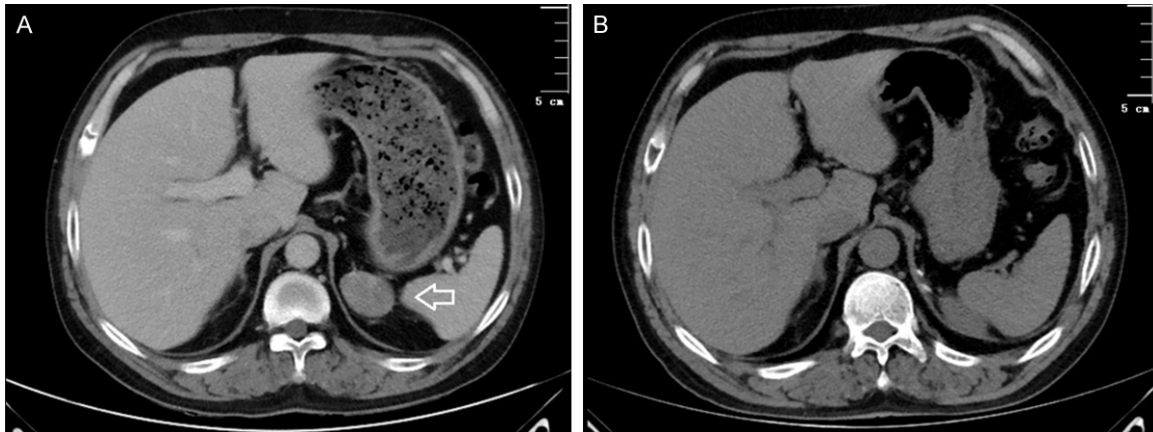


Figure 4. Computer tomography scan revealed a left adrenal mass that was removed by laparoscopic adrenalectomy. A: Abdominal computer tomography scan revealed a nodule in the left adrenal area (2.7*3.2*2.8 cm) (white arrow). B: Abdominal computer tomography scan suggest the nodule was removed by laparoscopic adrenalectomy.

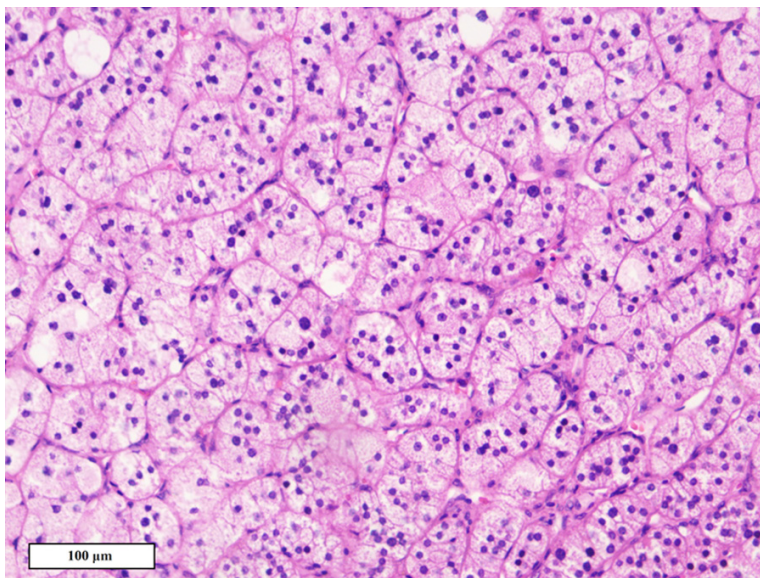


Figure 5. Microscopic findings of left adrenal mass (×400). Histopathologic examination showed cortical adenoma with lipid-rich clear cells resembling the zona fasciculata of normal adrenal gland.

(Figures 4B, 5) and was discharged with heart failure regimen including spironolactone 20 mg once daily, metoprolol 25 mg once daily and telmisartan 40 mg once daily. At the 12-month follow-up, he became asymptomatic and his blood pressure was well controlled. Reduction of heart size (LAD from 43 mm to 32 mm, LVEDD from 65 mm to 60 mm, RA from 38 mm to 30 mm, and RVD from 23 mm to 20 mm) and improvement of LVEF from 30% to 51%. The PAC was 87.88 pg/ml, the plasma renin concentration (PRC) was 39.02 μ IU/ml (range 4.7-47.6 μ IU/ml), and the PAC-to-PRC ratio was 2.2.

Discussion

It is reported that PA is more associated with severe diastolic dysfunction [6]. In PA patients, the most common cardiac pathological change is left ventricular remodeling, including LV enlargement, wall thickness, and concentric remodeling [7]. It is believed that slower LV filling, prolonged isovolumic LV relaxation, and increased diastolic LV stiffness contribute to increase LV wall stress and end-diastolic pressure, which are the central pathophysiological mechanisms of heart failure with diastolic dysfunction or preserved ejection fraction (HFpEF) [8]. In animal models, rats subjected to aldosterone

infusion have impaired LV diastolic function [9]. Rossi et al. showed that PA patients had lower E wave and A wave flow velocity ratio (E/A) integral ratio and atrial contribution to LV filling in echocardiograph [10].

However, relatively few studies have investigated the association between PA and heart failure with reduced ejection fraction (HFrEF) so far [4]. Cesari et al. reported PA patients had lower peak systolic septal strain and mid wall fractional shortening index than EH patients. However, this research was performed in those

Table 2. The prevalence of cardiovascular damage in primary aldosteronism patients

Author	Year	Sample (n)	Myocardial infarction (n, %)	Heart failure (n, %)	Atrial fibrillation (n, %)	Stroke (n, %)	Left ventricular hypertrophy (n, %)	Follow-up period
Puar TH [16]	2020	154	10 (6.9)	0	10 (6.9)	7 (4.8)	-	5.7+4.5 years
Xu Z [4]	2019	72						12 months
Confirmed PA		40	1 (2.5)	0	-	1 (2.5)	-	-
Probable PA		32	1 (3.1)	0	-	1 (3.1)	-	-
Huang WC [14]	2019	688	-	23 (3.3)	-	-	-	5.2+3.5 years
Ohno Y [25]	2018	2582	23 (0.9)	15 (0.6)	72 (2.8)	191 (7.4)	-	-
Murata M [26]	2017	292	7 (2.3)	6 (2.1)	8 (2.7)	30 (10.3)	-	-
Monticone S [27]	2017	99	15 (15.2)	-	-	-	20 (22.7)	-
APA		27	1 (11.1)	-	-	-	4 (17.4)	-
BAH		74	12 (18.8)	-	-	-	16 (27.6)	-
Savard S [28]	2013	459	20 (4.4)	19 (4.1)	18 (3.9)		-	-
Mulatero P [29]	2013	270	2 (0.7) [§]	1 (0.4)	2 (0.7)	28 (10.4)	-	12 months
Takeda R [30]	1995	224	4 (1.7)	8 (3.4)	-	14	-	

§: including myocardial infarction and unstable angina, APA: aldosterone-producing adenoma, PA: Primary aldosteronism, BAH: Bilateral adrenal hyperplasia, -: no data.

PA patients without clinical manifestations of systolic heart failure [11].

We report two systolic heart failure/HFrEF patients with PA due to BAH or APA, the most common subtypes of PA. It has been reported that, compared to EH patients, PA is associated with increased risk of stroke (odds ratio [OR] 2.58, 95% CI 1.93-3.45), atrial fibrillation (3.52, 2.06-5.99), coronary artery disease (1.77, 1.10-2.83) and heart failure (2.05, 1.11-3.78) [12]. The prevalence of CHF in PA patients is at least 0.6-4.1% as estimated (summary in **Table 2**), which might be underestimated because most of the data came from retrospective and case-matched studies. More importantly, all patients included in these studies already have received targeted therapy, either mineralocorticoid receptor antagonist (MRA) or adrenalectomy, which made it unclear why they developed new-onset HF.

In our study, two patients suffered from severe new-onset HFrEF associated with PA. Patient A was diagnosed with BAH and new-onset HFrEF, then received MRA therapy besides standardized HF treatment, which has been recommended by guidelines [13]. However, patient B with APA and new-onset HFrEF received laparoscopic adrenalectomy therapy besides standardized HF treatment. It is still controversial whether adrenalectomy is superior to ALD antagonists in APA patients. It has been reported that compared to the primary hypertension

control group, patients with APA underwent adrenalectomy lowered the risks of CHF, all-cause mortality [14], and incident rate of end-stage renal disease (ESRD) [15]. However, in patients with APA with MRA and without adrenalectomy, there was no statistically significant difference of the risks of developing CHF, or mortality, as compared with their respective EH controls [14]. On the contrary, Puar TH et al. reported that compared with adrenalectomy, medical therapy can offer similar cardiovascular protection (composite of previous acute myocardial infarction, coronary revascularization or coronary artery bypass graft, admission for congestive cardiac failure, atrial fibrillation [AF] or stroke) in patients with APA, and the surgery group only had lower pill burden [16]. Hundemer et al. found no statistically significant difference in PA patients who were only treated with MRA (in the renin increased [>1 ng/mL/h] group) and or adrenalectomy in terms of the risk of developing AF compared with EH controls [17]. This is also consistent with Catena et al.'s research result that the incidence of a composite endpoint (arrhythmia, myocardial infarction, coronary revascularization and stroke) did not differ between PA patients treated with spironolactone and those treated with surgery adrenalectomy [18]. In our study, it remains unclear whether their treatment might reduce the risk of mortality or re-hospitalization for HF which needs long-term follow-up to address this issue further.

The systolic function in our two patients markedly improved after targeted therapy, which may be due to multiple explanations. Firstly, this is probably because of a decrease of water and sodium retention that leads to preload reduction. Secondly, the target treatment for PA may reverse the aldosterone-induced myocardial fibrosis (carboxy-terminal propeptide of procollagen type I), which may also play a role [19]. However, we have noticed that the LVEF and LVEDD did not return to normal completely at the moment of follow up, even when the blood pressure, electrolyte levels and ALD were back to normal range. The same phenomenon was also observed by Sato et al. [5]. This might imply that myocardial fibrosis can be partially reversed only in the early stage of PA. This theory is supported by Xu et al., who found no significant difference in the prevalence of cardiovascular events between newly diagnosed PA patients with targeted treatment and the control group [4]. Lastly, correction of abnormal serum potassium, magnesium, and calcium levels may also benefit the improvement of heart function [20, 21], since these electrolyte abnormalities may worsen heart failure and arrhythmia, especially AF. It is worthy of noticing that these risks are independent of hypertension.

For our two patients with PA and HFrEF, there heart function significantly improved after getting target treatment for PA besides standardized treatment for HFrEF. There is a dilemma: Do they really need angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) and beta blockers? On the one hand, in heart failure guideline, ACEI/ARB and beta blockers are optimal medical management [22]. ACEI/ARB and beta blockers can inhibit the excessive and inappropriate renin-angiotensin-aldosterone action and decrease cardiovascular mortality. On the other hand, in PA guideline, ACEI/ARB and beta blockers are not the first choice for PA [22, 13], since plasma renin and angiotensin are already suppressed in PA. So far, there is still a lack of evidence regarding whether it is necessary to prescribe ACEI/ARB and beta blockers for PA patients with heart failure. Our cases provided some information that guideline-recommended heart failure treatment (ARB/ACEI, beta blocker, and MRA) after PA target treatment can continue benefit their heart function improve-

ment. But further research will be needed to answer how much effect ACEI/ARB and beta blockers can achieve in terms of the clinical improvement.

It has been reported that in patients with an adrenal incidentaloma (defined as adrenal mass detected on imaging performed for other reasons than suspected adrenal disease), the prevalence of PA is 1.6%-4.33% [23]. Thus, it is recommended to screen PA in patients with an adrenal incidentaloma according to current primary aldosteronism guidelines [23].

In conclusion, we reported two patients who presented with HFrEF as a result of hyperaldosteronism. One year after targeted therapy, heart function had markedly improved. Thus, in patients with heart failure and undetermined etiologies, it is important to screen PA, which can be treated appropriately and effectively.

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Both Zijun Chen and Zhe Zhang contributed equally to this work and should be considered as co-first authors. We thank Dr Kuai Yu for her assistance in pathology.

Disclosure of conflict of interest

None.

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