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Case Report

Unusual presentation of primary aldosteronism with advanced target organ damage: A case report

Cristiano Fava, MD, PhD^{a,*}, Filippo Cattazzo, MD^a, Riccardo Bernasconi, MD^b, Simone Romano, MD^a, Pietro Minuz, MD^a

^a Department of Medicine, General Medicine & Hypertension Unit, University of Verona, Piazzale LA Scuro 10, 37134 Verona, Italy

^b Department of Diagnostics and Public Health, Section of Pathology, University of Verona, Piazzale LA Scuro 10, 37134 Verona, Italy

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ABSTRACT

Patients with primary aldosteronism have greater cardiovascular morbidity and mortality than patients with primary hypertension and a comparable cardiovascular risk profile. Herein we present the case of a patient who developed multiple end-organ damage due to unrecognized and uncontrolled hypertension caused by an aldosterone-producing adrenal adenoma. Clinical and radiological evaluation revealed hypertensive encephalopathy, cardiomyopathy, retinopathy and nephropathy which required hemodialysis. Blood pressure control before surgery was difficult due to renal impairment that precluded the administration of anti-aldosterone drugs. Primary aldosteronism was cured by laparoscopic adrenalectomy and all antihypertensive drugs were suspended.

A remarkable aspect of this case is the discordant results at screening test for primary aldosteronism: even though aldosterone-to-renin ratio is the most reliable method to identify possible cases of primary aldosteronism it can be misleading especially in case of multiple comorbidities and concomitant antihypertensive treatment. Furthermore, anti-aldosterone drugs are worrisome to use when renal damage is advanced but can be reconsidered when hemodialysis begins.

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* Corresponding author.

E-mail address: cristiano.fava@univr.it (C. Fava).

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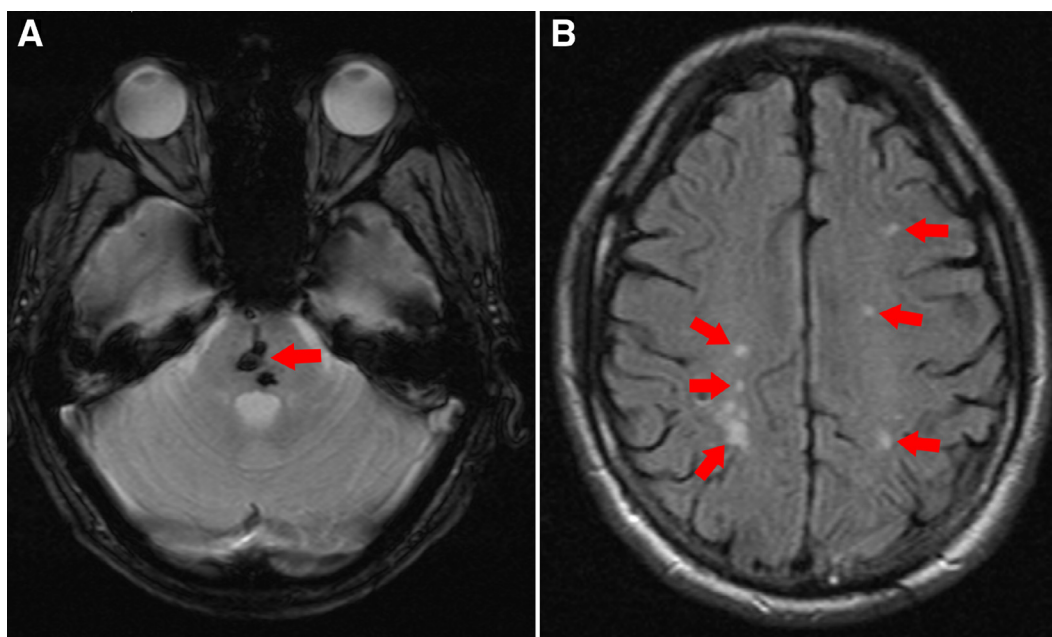


Fig. 1 – Nonenhanced brain magnetic resonance. (A) Axial T2-weighted gradient recalled echo sequence showing paramedian irregular hypointense spots in the encephalic trunk consistent with prior pontine hemorrhagic outcomes (arrow). (B) Axial T2-weighted turbo spin echo fluid attenuated inversion recovery sequence demonstrating diffuse hyperintense spots in the subcortical white matter with tendency toward confluence corresponding to areas of gliosis (arrows).

Introduction

Patients with primary aldosteronism (PA) are at higher risk of cardiovascular morbidity and mortality than patients with primary hypertension and a comparable cardiovascular risk profile [1]. Herein, we present a case of a patient who developed multiple end-organ damage due to unrecognized and uncontrolled hypertension caused by an aldosterone-producing adrenal adenoma. In particular, the diagnostic work-up and some issues about the choice of an effective antihypertensive therapy are described.

Timeline

| Timeline | Events |
|------------------------|--|
| Before hospitalization | Dizziness, headache, earache and vomiting |
| At admission | Uncontrolled BP, severe hypokalemia, impaired renal function |
| 2nd day | ARR: 102,7 |
| 4th day | Brain magnetic resonance showed hypertensive encephalopathy |
| 5th day | Echocardiography revealed hypertensive cardiomyopathy |
| 9th day | Abdominal magnetic resonance identified a left adrenal mass |
| 2nd week | Ophthalmoscopy showed malignant hypertensive retinopathy |

| | |
|-----------|---|
| 3rd week | ARR: 17,6 |
| 2nd month | The patient underwent hemodialysis |
| 4th month | Adrenal vein sampling confirmed unilateral disease |
| 6th month | A laparoscopic left adrenalectomy was performed |
| 7th month | Antihypertensive therapy was discontinued. Patient still on hemodialysis. |

ARR: p-aldosterone:p-renin ratio.

Case presentation

A 42-year-old white man, with a 1-year history of dizziness, headache, earache, and vomiting was hospitalized for a diagnostic work-up. His blood pressure (BP) was never measured in the preceding months. He took over the counter nimesulide for 6 months (on average 100 mg tid) and reported habitual use of recreational drugs (cocaine) and alcohol (on average 110 gr/d). Physical examination was unremarkable apart from a BP of 220/100 mm Hg and laboratory tests showed severe hypokalemia and impaired renal function (Table 1).

Assessment and diagnosis

Brain magnetic resonance showed findings consistent with hypertensive encephalopathy (Fig. 1) whereas echocardiography with hypertensive cardiomyopathy in dilatative phase (Fig. 2). At ultrasound, kidneys appeared of normal size and

Table 1 – Laboratory tests performed at hospital admission, during diagnostic work-up.

| Analytes | Results | Reference ranges |
|--|-----------------------------------|------------------|
| Hemoglobin (g/dL) | 7.8 | 13.5-17.0 |
| Mean corpuscular volume (fL) | 90.3 | 86.0-98.0 |
| Platelet (billion/L) | 116 | 150-400 |
| Blood urea nitrogen (mg/dL) | 150.1 | 17.1-47.1 |
| Serum creatinine (mg/dL) | 5.62 | 0.59-1.29 |
| Plasma potassium (mmol/L) | 2.25 | 3.40-4.80 |
| Inorganic phosphate (mg/dL) | 5.88 | 2.63-4.49 |
| Proteinuria (mg/24 h) | 560 | <30 |
| Urinary metanephrines (μ g/24 h) | 127 | 64-302 |
| Urinary normetanephrines (μ g/24 h) | 568 | 110-527 |
| PAC (pg/mL) | - at admission - 3 weeks later | 35.00-300.00 |
| ARC (pg/mL) | - at admission - 3 weeks later | 1.98-24.60 |
| ARR | - at admission - 3 weeks later | <32 |

ARC, active renin mass concentration; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration.

morphology and no renal artery stenosis was detected. Ophthalmoscopy revealed malignant hypertensive retinopathy (left eye; Fig. 3). Abdominal magnetic resonance identified a 22 mm left adrenal solid mass with typical features of an adenoma (Fig. 4), thus a presumptive diagnosis of PA due to an aldosterone producing adenoma was made, supported by the extremely high levels of aldosterone and aldosterone-to-renin ratio (Table 1). Adrenal vein sampling definitively confirmed unilateral disease showing an aldosterone/cortisol ratio of the left adrenal vein about 12 times greater than right/unaffected side.

Management

Forty mmol of potassium chloride in 1000 cc of normal saline were administered daily in order to reverse hypokalemia and

restore renal blood flow. BP remained initially elevated despite the administration of 3 antihypertensive drugs (amlodipine 10 mg/d, carvedilol 50 mg/d, and doxazosin which was gradually increased up to 16 mg/d). After a few days, i.v. furosemide 40-80 mg was added to the regimen and after plasma creatinine fell below 4 mg/dL, a trial with 25 mg/d of spironolactone was attempted but immediately interrupted for hyperkalemia and worsened renal function. Then, remaining BP values above 160/100 mm Hg, carvedilol was substituted by atenolol 100 mg/d observing a better BP control (on average <140/90 mm Hg). Although renal function slightly improved during hospitalization, the patient soon reached end stage renal disease that required hemodialysis.

Six months later a laparoscopic left adrenalectomy was performed. Histologic evaluation revealed an orange-colored cortical nodule with typical features of an adenoma (Fig. 5).

The postoperative period was uneventful and the patient was discharged with amlodipine 10 mg/d, atenolol 25 mg/d, doxazosin 2 mg/d, and furosemide 100 mg/d. All drugs were progressively discontinued due to the normalization of BP.

The effectiveness of surgery is proved not just by the withdrawal of all the antihypertensive drugs but also by the partial regression of cardiac structural abnormalities (Fig. 2). The patient was still on hemodialysis and work-up for renal transplantation began.

Discussion

PA usually leads to the development of moderate to severe hypertension [2] but with a greater cardiovascular morbidity and mortality than patients with primary hypertension and comparable cardiovascular risk profile suggesting that aldosterone excess prompts additional fibrosis and remodeling in target organs [1,3]. Furthermore, aldosterone hypersecretion can lead to significant functional changes in the kidney, such as an increase in renal perfusion pressure, which are largely

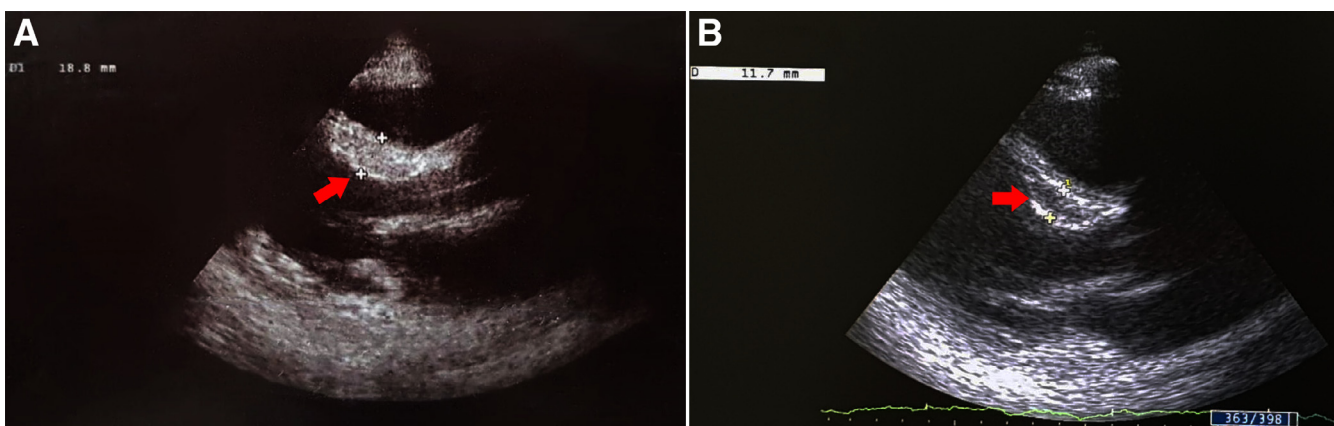


Fig. 2 – Transthoracic echocardiogram. (A) Parasternal long axis view showing an interventricular septum thickness of 18.8 mm (arrow) at 5 days after admission. Left ventricular mass indexed to body surface area was 188 gr/m² demonstrating pronounced left ventricular hypertrophy. (B) Parasternal long axis view showing an interventricular septum thickness of 11.7 mm (arrow) at 7 months after hospitalization.



Fig. 3 – Fundus photographs showing papilledema (arrow) (A), cotton wall spots (arrow) and flame hemorrhage (arrowhead) (B).

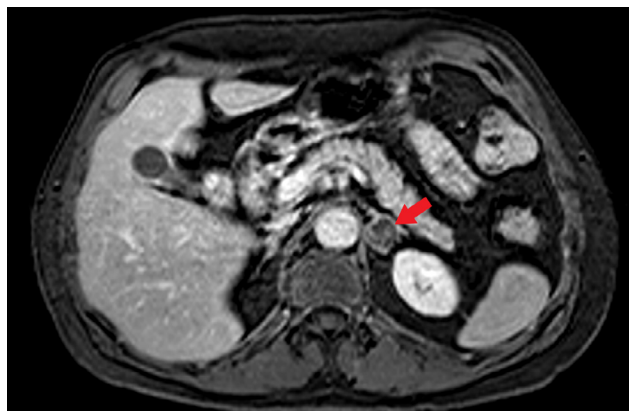


Fig. 4 – Contrast-enhanced abdominal magnetic resonance. Axial T1-weighted 3D GRE fat sat sequence after administration of contrast agent (portal venous phase) showing a round adrenal mass (arrow) with well demarcated margins and lipid content, with capsular and thin septal enhancement.

reversible in the earliest stages of the disease but later can result in nephroangiosclerosis and progressive kidney injury [4].

Cardiovascular and renal complications in patients with PA generally require many years to occur but the patient described herein, despite his relatively young age, developed multiple end-organ damage at presentation. Thus, we can speculate that either his clinical history was longer than recorded, or that hypertension and PA were particularly severe or that other factors such as cocaine, alcohol, and nonsteroidal anti-inflammatory drugs abuse can have contributed. As known, chronic cocaine abuse can be related with an increase in left ventricular mass index [5] and diastolic dysfunction

[6] and nonsteroidal anti-inflammatory drugs abuse can have harmful effects on renal function that may cause disease progression in patients with pre-existing kidney disease [7].

Another interesting issue is the possible confounding effects of plasma renin and aldosterone given by the therapy on one side and nephroangiosclerosis on the other. It is worth noting that in the first dosage aldosterone was extremely high but renin not correspondently inhibited probably due to the stimulus derived by the chronic kidney disease [4] or the relative patient's dehydration. After three weeks of antihypertensive therapy, including beta-blockers (renin inhibitor), furosemide (renin stimulator) and amlodipine (slight renin stimulator) other than abundant hydration (renin inhibitor) [1] but still in a situation of nephroangiosclerosis (renin stimulator) [4], aldosterone was almost normalized and renin persisted not suppressed. This underlines the importance of the careful consideration of the different factors that can either inhibit or enhance renin and aldosterone production to pursue a correct diagnosis. Of note, a second line test to rule out primary aldosteronism, due to concomitant renal comorbidity, was not advisable.

Despite the initial institution of a quadruple antihypertensive therapy, the patient presented resistant hypertension. Furthermore, due to the development of end stage renal disease, administration of mineralocorticoid receptor antagonists, the drugs of choice in the medical treatment of PA, was not possible before hemodialysis [1]. Some studies show that anti-aldosterone drugs can be administered safely in patients undergoing hemodialysis [8,9], but the cure of hypertension after aldosterone removal did not require its use herein. Moreover, satisfactory BP control, until surgery, was obtained by replacing carvedilol with atenolol. In general, nonlipophilic beta-blockers, such as atenolol, are excreted unchanged in the urine [10] whereas lipophilic agents, such as carvedilol, are subject to extensive first-pass metabolism dependent on cy-

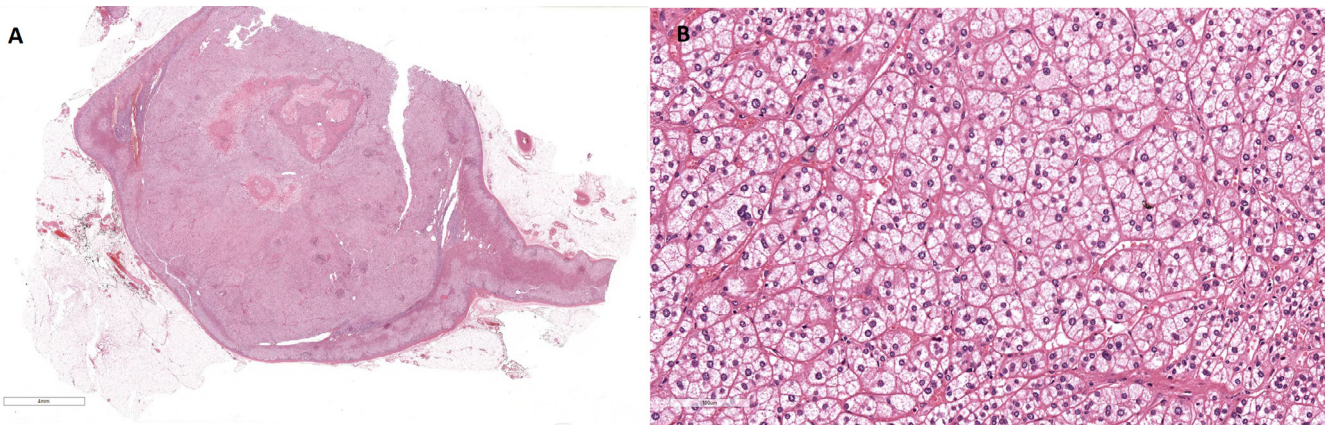


Fig. 5 – Histologic images. (A) Adrenal gland with adenomatous proliferation. (B) Details of cellularity referred to the adenomatous proliferation (H&E, 20x).

tochrome P450 2D6 enzyme. The interindividual differences in isoenzyme activity may considerably affect metabolic rate of lipophilic beta-blockers resulting in ineffective blood levels in some rapid or ultra-rapid metabolizers [11]. Therefore, in this patient, the much more reliable bioavailability of hydrophilic beta-blockers could explain the greater antihypertensive effect of atenolol compared to carvedilol.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.radcr.2019.04.011](https://doi.org/10.1016/j.radcr.2019.04.011).

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