Case Report

A case with primary hyperaldosteronism associated with chronic kidney disease

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Abstract

Primary hyperaldosteronism (PA) is one of the most common causes of secondary hypertension. PA may be associated with a decline in renal function. About 20% of cases with resistant HTN eventually cause PA, so all these patients should be evaluated for PA. Herein, we present a case with drug-resistant hypertension and chronic kidney disease (CKD), the cause of which was PA. Despite his low-salt diet modifications and treatment with several classes of antihypertensive medication, he had poorly controlled blood pressure (BP). Measurements of aldosterone and renin raised the concern of PA. Imaging confirmed bilateral adrenal hyperplasia. Due to the persistently high BP, despite the modification of the antihypertensive treatment, the patient underwent unilateral adrenalectomy, as the only feasible possibility of lowering aldosterone levels. After surgery, the patient had an improvement in both BP values and renal function. PA is difficult to diagnose in patients with CKD and Arterial Hypertension because hypertension is often associated with CKD, but PA accounts for a

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significant percentage of drug-resistant hypertension, so these patients should be screened for secondary arterial hypertension.

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Introduction

Primary aldosteronism (PA), or Conn Syndrome, is the most common cause of secondary hypertension. There is a prevalence of approximately 4% in the outpatient setting of patients with hypertension and about 10% in hypertensive patients referred to tertiary hospital centers [1]. PA affects 10% of patients with moderate hypertension and 20% of those with drug-resistant hypertension [2]. The most common causes of PA are adrenal adenoma (40%) and bilateral adrenal hyperplasia (60%); however, more rare causes include adrenal adenocarcinoma, ectopic aldosterone secretion by the kidney or ovary, or unilateral adrenal hyperplasia [3]. The prevalence of adrenal adenoma (AA) is higher in women than in men (70% of women) and is located more often in the left adrenal gland. Bilateral adrenal hyperplasia (BAH) occurs with an equal frequency in both women and men [4]. Prompt diagnosis and treatment of PA in hypertensive patients are critical since patients with PA have a higher risk of cardiovascular complications than patients with essential hypertension [5]. Aldosterone is important in maintaining homeostasis in patients with hypertension and electrolyte disorders, but it also increases the risk of cardiovascular, cerebrovascular, and metabolic complications, exposing various organs to its proinflammatory effects [6].

Case report

A 58-year-old man presented to the hospital with headache, bulbar eye pain, vertigo, limb ataxia, chest pain, and shortness of breath. These complaints had been present for 2 months, with progressive deterioration in the previous week, and were associated with extremely high blood pressure (BP of 260/120 mmHg), despite titration of his blood pressure treatment regimen. He was currently on treatment with Losartan/ HCT (50/25) mg, Bisoprolol 10 mg, Amlodipine 10 mg, Moxonidine 0.4 mg, daily.

His past medical history revealed a history of recurrent renal calculi and hypertension treatment for ten years, for which the patient had become resistant to treatment in the previous 2 years. There was a family history of drug-resistant arterial hypertension and stroke, both of which resulted in death at a young age.

His vital signs during hospitalization were as follows: BP = 240/110 mmHg; HR = 62 beats/min; Temp = 36.5 °C, RR =16 / min, and SpO2 = 97% on room air. Laboratory studies revealed increased blood urea nitrogen (BUN) at 72 mg/dL (normal range 20-44 mg/dL), increased serum creatinine at 1.7 mg/dL (0.6-1.2 mg/dL), albuminuria at 750 mg/dL (0-30 mg/dL/24h), decreased GFR 42 ml/min/1.73 m² (80-120 ml/min/1.73 m²) and a potassium level at the lower limit of the reference range 3.5 mEq/L (3.5-5.1 mEq/L).

Imaging examinations including a cardiac ultrasound revealed left ventricular hypertrophy with a normal EF (ejection fraction) 55% and increased interventricular septal thickness 12.5 mm [6-11]. The ECG showed a sinus rhythm. The abdominal ultrasound was normal, with no evidence of renal pathology. Doppler ultrasound ruled out the possibility of renal artery stenosis.

ABPM (Ambulatory blood pressure monitoring): Optimal 8%; Normal 25%; Normal increased 18%; Grade I 18%; Grade II 11%, Grade III 6%, isolated systolic 14%. The fundoscopic examination revealed initial hypertensive retinopathy.

His antihypertensive therapy was initially modified. He was prescribed diuretics in addition to Hydrochlorothiazide, Furosemide IV, Carvedilol, Nifedipine, Ramipril, Moxonidine were added, as well as Doxazosin, but BP levels were persistently high (Max – 190/ 100 mm), in these conditions despite the presence of CKD, so a secondary etiology of hypertension was suspected.

The morning of the patient’s admission, hormonal testing showed normal levels of cortisol, ACTH, plasma catecholamines and Chromogranin A, but an increased aldosterone/renin ratio of 21.6, increased aldosterone levels 19.5 ng/dL(1.6-16 ng/dL), and elevated levels of urine metanephrines 377.5 ug/24h (44-261 ug/24h). Significant elevation of urine metanephrines were present at the highest BP value. The suppression of cortisol levels in the morning after 1 mg dexamethasone administration at midnight ruled out Cushing’s syndrome.

A diagnosis of primary hyperaldosteronism was suspected due to persistent hypertension despite treatment with ARB, ACE-inhibitors, diuretics, and other antihypertensive medications. As a result, a contrast-enhanced CT of the abdomen was performed.

Abdominal CT with IV contrast revealed the left adrenal gland was hyperplastic with the transverse diameter up to 7 mm and the presence of a hypodense micronodule with a 5 mm diameter. (Fig. 1, Fig. 2)

Despite the premedication performed before CT, the patient manifested CIN (contrast nephropathy) with serum creatinine levels up to 2.2mg/dl. After treatment, levels decreased within the normal range. We could not obtain phlebography of the adrenal glands with selective venous catheterization as this method is not performed in our hospital.

Antihypertensive therapy was re-evaluated in the context of the diagnosis of PA where thiazide and loop diuretics were replaced with spironolactone and continuation of ACE-inhibitors, B-blockers, calcium channel blockers, and central alpha agonists.

On account of a CT confirmation of bilateral adrenal hyperplasia, findings of an increased aldosterone/renin ratio, along with the inability to perform other diagnostic tests (adrenal...
Fig. 1 – Abdominal coronal CT images with IV contrast (Fig. A and B) demonstrates left adrenal gland hyperplasia (red arrows) before the unilateral subtotal left adrenalectomy (Color version of figure is available online)

phlebography with selective venous catheterization) in our hospital, we decided the best treatment approach to decrease serum aldosterone levels and consequently, achieve control of the high blood pressure values, was a unilateral subtotal left adrenalectomy. Our patient had hypertension-mediated cardiovascular, ocular, and renal manifestations in the context of primary aldosteronism (PA).

The patient underwent left laparoscopic adrenalectomy. Histopathological findings of the obtained material confirmed cortical hyperplasia and the absence of malignant adenomatous or neoplastic elements.

At the 3-month follow-up, he had a decrease in BP values (Max 150/85 mmHg) with his current treatment of Nifedipine, Spironolactone, and Ramipril. Post-operative laboratory examinations revealed a reduction of proteinuria to 300mg/dl/24h, improvement of GFR to 52 ml/min/1.73m2, and normal levels of potassium were observed.

Discussion

Resistant HTN is defined as the persistence of high BP values in patients treated with at least 3 classes of antihypertensive medications (in which at least one of the classes must be a diuretic) including: Ca channel blocker, β-blocker, ARB or ACE inhibitor, and diuretics. Studies have shown that in about 20% of cases with resistant HTN, the culprit is Primary Aldosteronism (PA). Thus, all patients presenting with drug-resistant arterial hypertension, should be screened for PA. Positive screening tests include an aldosterone/renin ratio > 30 or >20 if the aldosterone level is ≥ 16/ ng/dL.[7]

PA was once thought to be a rare etiologic factor of hypertension, but it is now the most common cause of secondary hypertension [8]. Recent studies for PA show an increase in cardiovascular and cerebrovascular morbidity and mortality, with a worse prognosis than for primary hypertension, even in cases of PA where blood pressure is completely controlled [9]. Hence, early detection of PA among hypertensive patients is crucial, to ensure a better long-term prognosis and prevent secondary sequelae. However, early diagnosis of PA is challenging, due to the lack of typical biochemical anomalies, such as hypokalemia (present in only 37% of patients with PA) [10] and specific imaging findings. Often, owing to the very small dimensions of adenomas and hyperplastic lesions, imaging findings in CT or MRI are elusive, making a diagnosis of PA more difficult to establish [11].

PA is usually diagnosed at the age of 30 to 50 years, although there are sporadic cases of late manifestation of the disease [12]. PA is considered to be underdiagnosed in common clinical practice. In our case report, although the patient did not present within the typical age bracket (58 years old), suspicion arose due to the hypokalemia aggravated by the use of non-potassium sparing diuretics in a CKD subject [10] and positive anamnisis for stroke in 2 of his family members (mother and uncle) which resulted in death at a young age of 55 years old, as well as, evidence of drug-resistant HTN and uncontrolled BP values even after modification and treatment with more than 4 classes of antihypertensive medication. The retrospective study performed on strokes
showed that the incidence of strokes associated with PA was much higher (12.9%) than strokes caused by primary hypertension (3.4%) when comparing groups between 124 patients with PA and 465 patients with primary hypertension. Both groups had similar age, sex, and mean blood pressure 175/107 mmHg [9]. Since the patient was being treated with several classes of antihypertensive medications that interfered with catecholamine measurements and at peak BP the level of catecholamines was normal, the diagnosis of pheochromocytoma was not considered [13].

Curiously, during physical examination (cardiac palpation and fundus oculi), our patient presented with target organ damage, predominantly affecting the heart. The myocardial changes stem from the effects of decade-long uncontrolled hypertension (indirectly) and the presence of primary aldosteronism (directly). The funduscopic examination, on the other hand, revealed first-grade hypertensive retinopathy, alone. These findings suggest that PA is the main factor contributing to these pathological changes since long-term exposure to HTN would have caused more severe retinopathy.

Long-term exposure to elevated levels of aldosterone is associated with organ damage independent from hypertension. Primary aldosteronism induces fibrosis in multiple organs including the heart, kidneys, adrenal glands, pancreas, and lungs [13]. Myocardial fibrosis contributes to the development of arrhythmias and heart failure [13]. Studies show that metabolic syndrome is more prevalent in this population, compared to patients suffering from essential hypertension, thus supporting the hypothesis that PA exerts some influence on metabolism [13]. Elevated aldosterone promotes the development of hypertension through water and salt retention, as well as by remodeling the vasculature of important organs such as the heart and kidneys, due to its proinflammatory activity [6,13].

Identifying and diagnosing PA among patients with renal involvement remains challenging both for its atypical clinical presentation and oftentimes ambiguous imaging findings. PA remains an underestimated cause of resistant hypertension in common clinical practice, despite it being the most common cause of secondary hypertension [14]. Hormonal dosing (aldosterone and renin) along with electrolyte testing should be implemented in protocols for diagnosing the etiology of drug-resistant hypertension and among patients with renal involvement thus preventing cardiovascular, cerebrovascular and metabolic complications and improving the quality of life in these patients.

**Conclusion**

In patients with chronic kidney disease, hypertension is a common comorbidity that reduces life expectancy and quality of life. The purpose of this case report is to assess and emphasize the importance of recognizing primary aldosteronism (PA) as the most common cause of secondary hypertension and in particular the main cause of drug-resistant hypertension. Diagnosis of PA among patients with renal involvement should focus beyond the typical age range and serum potassium levels, to allow for a timely diagnosis and appropriate management, as to prevent serious cardiovascular and cerebrovascular complications.

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**Fig. 2 – Axial CT images (A, B) demonstrating non-tumoral enlargement of left adrenal gland (yellow arrows) and right adrenal gland (orange arrows) (Color version of figure is available online)**
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