CASE REPORT

Resistant Hypertension: A Diagnostic Challenge

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ABSTRACT:

Introduction: Primary hyperaldosteronism is a leading cause of secondary arterial hypertension, affecting approximately 10% to 20% of the hypertensive population worldwide and in Brazil. This condition involves excessive aldosterone production due to factors such as adrenal adenoma, hyperplasia, or, less commonly, adrenal carcinoma and familial hyperaldosteronism. This study reports a case of resistant hypertension secondary to aldosterone-producing adenoma.

Clinical Case: A 70-year-old male patient presented with episodes of dizziness, syncope, cramps, and asthenia. His medical history included resistant hypertension for over 30 years, despite treatment with five classes of antihypertensive medications. Additionally, he had a history of dyslipidemia, type 2 diabetes mellitus, non-dialysis chronic renal failure, and obstructive coronary artery disease. Physical examination showed a BMI of 29 kg/m² (overweight), mean blood pressure of 140/90 mmHg (right arm) and 150/100 mmHg (left arm), and palpable nodules in both thyroid lobes, classified as Bethesda V based on aspiration cytopathology. Subsequently, he underwent total thyroidectomy and lymph node dissection. Laboratory tests revealed high plasma aldosterone levels with suppressed renin and an elevated aldosterone-renin ratio, raising suspicion of primary hyperaldosteronism. This diagnosis was confirmed by a computed tomography scan, which identified a 1.2 cm nodule in the right adrenal gland consistent with an adenoma. The patient underwent unilateral laparoscopic adrenalectomy. Two years post-surgery, the patient's blood pressure was well-controlled with three antihypertensive medications, and his blood sugar, aldosterone, and renin levels were normal.

Discussion and Conclusion: Most patients undergoing unilateral adrenalectomy for aldosterone-producing adenomas experience significant clinical improvement. Early screening and diagnosis of primary hyperaldosteronism are crucial for effective management, reducing the risk of complications in the cardiovascular and renal systems.

Keywords: Hyperaldosteronism, Hypertension, Delayed diagnosis

INTRODUCTION

Resistant arterial hypertension (RAH) is characterized by the persistence of blood pressure (BP) of 140/90 mmHg or higher, despite the use of three or more antihypertensive medications, including a thiazide diuretic. It is estimated to affect 12 to 15% of individuals with hypertension. While various factors can contribute to this condition, secondary causes are more prevalent among those with hypertension that is resistant to treatment[1].

Secondary hypertension is defined by arterial hypertension (AH) with a specific, identifiable cause that can be addressed through targeted intervention, often resulting in improved blood pressure control or even cure. Resistant hypertension represents a high-risk phenotype, associated with increased all-cause mortality and adverse cardiovascular disease (CVD) outcomes[2]. Among the various causes, primary hyperaldosteronism (PH) is a significant pathology contributing to resistant arterial hypertension (RAH). PH encompasses disorders characterized

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by inappropriately high aldosterone production that is relatively independent of the renin-angiotensin system and not suppressible by sodium intake. This condition leads to cardiovascular damage, suppression of plasma renin activity (PRA), hypertension, sodium retention, and increased potassium excretion. If prolonged and severe, it can result in hypokalemia[3].

From an etiological perspective, bilateral adrenal cortical hyperplasia (CAH) is the most common cause of primary hyperaldosteronism (PH), followed by aldosterone-producing adenomas (APA). In rare instances, PH may be caused by adrenal carcinoma or hereditary conditions of familial hyperaldosteronism[1,3,4]. Most patients with PH are asymptomatic, while others may present symptoms related to hypertension such as headache, palpitations, hypokalemia, polyuria, nocturia, cramps, tetany, and paresthesia[5].

This clinical report presents the case of a male patient with resistant hypertension compatible with primary hyperaldosteronism.

CLINICAL CASE

A 70-year-old male patient with melanoderma and resistant hypertension for over 30 years, despite daily use of multiple antihypertensive medications (chlorthalidone 25 mg, amiloride 5 mg, valsartan 320 mg, amlodipine 5 mg, nebivolol 5 mg, and hydralazine 100 mg), was referred to a specialized endocrinology service for evaluation of secondary causes of his hypertension. He reported frequent dizziness, occasional syncope, asthenia, and persistent cramps on the symptomatology questionnaire.

Since 2010, he has been diagnosed with dyslipidemia and is on rosuvastatin 20 mg daily. In 2012, he was diagnosed with non-dialytic chronic renal failure (CRF), which is under clinical control. In 2013, he was diagnosed with type 2 diabetes mellitus and began treatment with metformin hydrochloride XR 750 mg/day, insulin glargine 10 IU/day, gliclazide MR 60 mg/day, and dapagliflozin 10 mg/day. He also has a history of obstructive coronary artery disease with significant lesions in the left coronary territory, having undergone angioplasty in 2013 with the placement of 2 stents, followed by pulmonary thromboembolism. Since then, he has been taking isosorbide mononitrate 40 mg/day and acetylsalicylic acid 100 mg/day. In 2014, he underwent catheterization and angioplasty to further assess his coronary artery disease.

Regarding his family history, the patient reports being adopted. He denies alcoholism, smoking, and illicit drug use. He follows a balanced diet low in sodium, glycemic index, and protein, with adequate water intake, and reports normal sleep patterns.

On physical examination, he appeared in good general condition, active, with atypical facies, normochromic, acyanotic, and anicteric. Anthropometric measurements showed a BMI of 29 kg/m² and an abdominal circumference of 100 cm. Peripheral pulses in both upper and lower limbs were symmetrical and palpable. Blood pressure measurements were as follows: right arm in the supine position 140/90 mmHg; left arm in the supine position 140/80 mmHg; sitting 140/100 mmHg; and orthostatic position 140/90 mmHg.

Thyroid examination revealed increased gland volume with a fibroelastic appearance and painlessness on palpation, along with palpable nodules in both lobes. Car-

diovascular examination showed a palpable ictus cordis with mobility at 2 digital pulses, a normal heartbeat with two clicks, regular rhythm, and a heart rate of 80 bpm. Respiratory auscultation revealed vesicular breath sounds without abnormalities. Abdominal examination showed no visceromegaly or abnormal murmurs. Extremities had symmetrical and palpable peripheral pulses, and a normal Achilles reflex was noted.

On his follow-up visit, complementary tests were requested. The initial laboratory tests are described in Table 1 and the captopril test is shown in Table 2.

Table 1- Initial laboratory tests and 2 years after left adrenalectomy.

Laboratory parameters	Initial tests	Tests 2 years after left adrenalectomy
Fasting blood glucose	106 mg/dL	91 mg/dL
Postprandial blood glucose	85 mg/dL	168 mg/dL
Glycated hemoglobin	7.2%	6.1%
TSH	2.3 µUI/L	2.04 µUI/L
Free T4	0.9 µUI/L	0.6 µUI/L
Aldosterone	27.9 ng/mL	1.8 ng/mL
PRA	0.77 ng/mL	1.1 ng/mL
Aldo/PRA	42	1.6
Potassium	3.2 mmol/L	4.0 mmol/L
Urinary aldosterone	38.8 ug24h	-
Urinary metanephrines	1.03 mg/24h	-
Microalbuminuria	426 mg/dL	-
Creatinine clearance	60.4 mL/m² /SC	47.8 mL/m² /SC

Table 2 - Dynamic captopril test to assess primary hyperaldosteronism.

Test	Aldosterone (ng/mL)	PRA (ng/mL)	18 OH Corticosterone (ng/mL)
Basal	28.6	1.3	120
2 hours	26.8	1.1	150

*The Captopril Test is based on the oral administration of 25 or 50 mg of Captopril, in a single dose, after the individual has been sitting or standing for at least 1 hour. Blood samples are taken to measure aldosterone, renin and cortisol, before and 1 or 2 hours after administration of the drug. In healthy individuals or those with essential hypertension, aldosterone is often reduced by more than 30% after captopril. In cases of PH, aldosterone will remain high and renin suppressed[5].

In imaging tests, thyroid ultrasound (US) showed two hypoechoic nodules in the left and right lobes, total abdominal US showed polycystic kidneys and abdominal CT showed a small 1.2 cm nodule in the right suprarenal (SR) gland compatible with adenoma, as shown in figure 1.

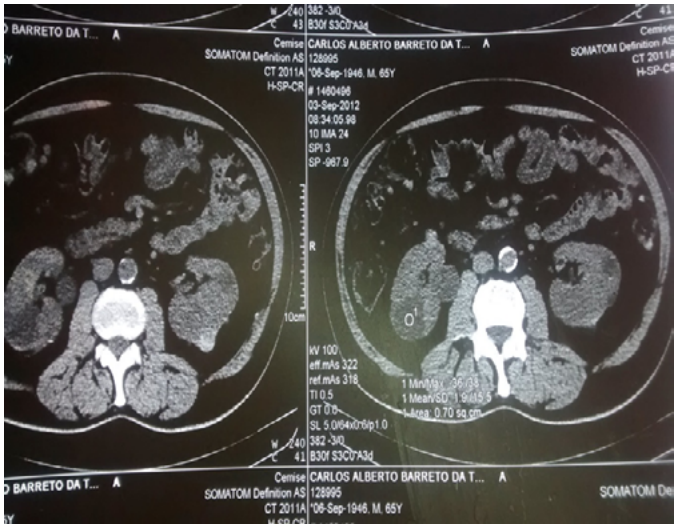

Figure 1- Thin-section CT scan of the suprarenal glands.

Subsequently, laparoscopic adrenalectomy was chosen because it was a single nodule in the right SR. The material was sent for anatomopathological analysis, with the following findings: a fragment of adrenal tissue with nodular thickening of the cortex without atypia and fragments of adipose tissue with vascular ectasia, which may correspond to adrenal cortical hyperplasia or adenoma.

Two years after treatment, the patient had well-controlled hypertension, using amlodipine 2.5 mg/day, valsartan 80 mg/day, and hydrochlorothiazide 25 mg/day. He had non-dialytic CRF under clinical control. She was also taking clopidogrel 75 mg/day, rosuvastatin 20 mg/day, and dapagliflozin 10 mg/day to treat pulmonary thromboembolism, dyslipidemia, and DM2, respectively.

Laboratory tests two years after starting treatment showed a decrease or normalization of biochemical and hormonal parameters, as illustrated in Table 1.

DISCUSSION

According to the Pan American Health Organization (PAHO), arterial hypertension (AH) is responsible for more than 50% of cardiovascular diseases (CVD)[6]. In Brazil, according to the Ministry of Health, the pathology affects more than 30 million individuals[7]. However, only a small percentage of patients with hypertension reach the ideal blood pressure level due to underdiagnoses and inadequate treatment of secondary causes of hypertension, such as PH[8].

Several studies indicate that around 20% of patients with resistant hypertension have primary hyperaldosteronism[9,10]. In addition, lower levels of excess aldosterone, which do not meet the criteria for classic PH, can influence resistance to conventional antihypertensive drugs[11]. This increase in aldosterone may be linked to obesity, a frequent comorbidity in patients with resistant hypertension[12]. It is therefore suggested that the accumulation of abdominal fat, which is more common in men, may directly release aldosterone or indirectly stimulate the release of aldosterone secretagogues[13,14].

Although there is a high prevalence reported in studies, patients with hypertension are rarely screened for PH[2]. This is because it typically presents as normocalemic hypertension, with hypokalemia occurring in only 20% of cases [15]. This makes it necessary to raise awareness of primary aldosteronism and its screening indications in primary and tertiary care, avoiding a late diagnosis that could lead to complications and damage to target organs, with a significant impact on public health costs[16]. In 2018, AH was the main factor responsible for spending (US$ 523.7 million) within the Unified Health System (UHS)[1].

A meta-analysis study by Chen et al (2011)[17] showed that one-fifth of patients with primary aldosteronism suffer from abnormal glucose metabolism. It is reported in the literature that high plasma aldosterone levels can lead to hypokalemia, with a consequent reduction in insulin secretion and the appearance of insulin resistance[18].

The diagnostic approach for PH is carried out in three stages: screening, confirmation and differentiation between the subtypes. Screening criteria include patients with hypertension, and spontaneous hypokalemia or hypokalemia caused by diuretics, those resistant to the usual treatments, or those with abdominal tumors. Screening should be carried out by measuring plasma renin activity (PRA), and plasma aldosterone concentration and calculating the aldosterone/PA ratio (ARR), with prior correction for hypokalemia[4,5]. To avoid false-negative results, diuretics and spironolactone should be discontinued 4 to 6 weeks in advance[19].

According to the VI Brazilian Hypertension Guidelines[1], the finding of RAR ≥ 30 with serum aldosterone > 15 ng/dl is suggestive of PH, requiring further investigation. In the case reported above, the association of these criteria with resistant hypertension and hypokalemia leads to primary hyperaldosteronism as the main diagnostic hypothesis.

In a study carried out in Italy with 1,672 individuals with hypertension, a total of 5.9% of patients had PH, of which 64.6% had HBP. At the same time, the study reports that the prevalence of PH is largely underestimated in this population[20]. In this sense, a more comprehensive use of screening tests would be more efficient in capturing these patients, in order to guarantee an earlier diagnosis[21].

Confirmation of the case can be made through suppression tests in which the absence of an aldosterone response serves to prove the autonomy of its secretion. The tests used include oral sodium overload, which was the option of choice in this case, as well as saline solution infusion, oral administration of fludrocortisone or intravenous furosemide, or the captopril test[2,4,5].

After diagnosis, thin-section computed tomography (CT) or magnetic resonance imaging is necessary to differentiate hyperplasia from adenoma and to exclude large adrenal masses compatible with carcinoma. Another test used to differentiate between APA and HAB is adrenal vein catheterization, the purpose of which is to simultaneously collect aldosterone and cortisol to identify the source of aldosterone secretion. The postural test is a non-invasive procedure that is also useful in differentiating between APA and HAB[2,4,5].

Regarding treatment, the best choice for those with aldosterone-producing adenoma or unilateral adrenal hyperplasia is surgical removal of the adrenal gland via a laparoscopic approach. After a unilateral adrenalectomy, most patients experience correction of hypokalemia and a moderate improvement in blood pressure. In the cohort study by Hannon et.al (2017), a large proportion of patients (94%) obtained clinical benefit, with significant improvements in blood pressure control, normalization of serum potassium, plasma renin and plasma aldosterone levels and reduction or elimination of antihypertensive therapy after unilateral adrenalectomy[22].

For those who cannot undergo surgery or have bilateral adrenal hyperplasia, mineralocorticoid antagonists such as spironolactone or eplerenone are a viable option. A randomized study evaluated the antihypertensive effect of spironolactone *versus* eplerenone in patients with primary hyperaldosteronism and found that spironolactone was more effective in controlling blood pressure[9,23]. In addition, other antihypertensive drugs can be continued as needed to optimize blood pressure control.

CONCLUSION:

The clinical case highlights the importance of investigating secondary causes when resistant hypertension is present, to enable early diagnosis and treatment. In cases of unilateral primary hyperaldosteronism, surgery is the preferred approach and has shown favorable outcomes in terms of blood pressure control.

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