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Case Report

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A secondary hypertension case report

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Abstract

A 46 years old patient was admitted to our clinic for progressive shortness of breath for two months, palpitations and headache. The patient was a smoker (20 packages/year) and had a history of dyslipidemia and arterial hypertension for a year. He has been taking three antihypertensives. The blood pressure in supine position was 190/100mmHg equally bilateral.

The blood tests showed: mild hypokalemia (K 3.1mmol/L). The echocardiography revealed left ventricular hypertrophy, predominantly of the septal wall (12-13mm), without enlargement of the left ventricle and a normal systolic function (55% ejection fraction). Taking into consideration the resistant arterial hypertension in a young patient despite three antihypertensive drugs, a diagnostic work-up for secondary hypertension was initiated. The associated hypokalemia raised the suspicion of hyperaldosteronism.

The serum level of aldosterone and renin were detected and the ratio between them showed a hypersecretion of aldosterone. An abdominal CT scan was performed and excluded an adrenal mass or another morphological causes that could emerge to hyperaldosteronism (renovascular causes, renin producing tumors, etc). Consequently, the final diagnostic was idiopathic primary hyperaldosteronism.

In our case, the primary aldosteronism it is not associated with a specific secreting mass and thus surgery was not an option. The medical treatment remained the most suitable solution that can adjust the blood pressure values.

The patient received Spironolactone 50mg od and Olmesartan/Amlodipine 40/5mg od, having a good outcome regarding blood pressure control.

Keywords: primary hyperaldosteronism, resistant arterial hypertension, mineralocorticoid receptor antagonist

A 46 years old patient was admitted to our clinic for progressive shortness of breath for two months, palpitations and headache. The patient was a smoker (20 packages/year) and had a history of dyslipidemia and arterial hypertension for a year. He has been taking three antihypertensives (amlodipine 10mg od, indapamide 1.5mg od, enalapril 20mg bid). He denied any angina or syncope.

Clinical exam: his heart rate was irregular, at 100beats/minute. There were no signs of cardiac congestion and the lungs were clear to auscultation. The blood pressure in supine position was 190/100mmHg

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equally bilateral, without any significant dropping after three minutes of orthostatic position.

The blood tests showed: mild hypokalemia (K 3.1mmol/L), normal renal and liver function, spot urine sodium 51mmol/day, potassium 35.3 mmol/day.

Electrocardiogram on admission showed atrial fibrillation, voltage criteria for left ventricular hypertrophy, without any electrical signs of ischemia.

A chest X-ray was performed at the time of admission and was unremarkable.

The echocardiography revealed left ventricular hypertrophy, predominantly of the septal wall (12-13mm), without enlargement of the left ventricle and a normal systolic function (55% ejection fraction). The transmitral Doppler pattern showed a grade 1 diastolic dysfunction with increased filling pressures and a dilated left atrium (70ml/m^2). No significant valve disease was identified and there was no evidence of increased pulmonary artery pressure.

The cardiac MRI showed left ventricular hypertrophy, normal ventricular walls contraction and normal systolic function. (figure 1 A, B and C). Multiple mid-myocardial focal scars were seen in the basal segments of the lateral and anteroseptal walls (figure 1 D).

Taking into consideration the resistant arterial hypertension in a young patient despite three antihypertensive drugs, a diagnostic work-up for secondary hypertension was initiated. The associated hypokalemia raised the suspicion of hyperaldosteronism.

An Abdominal Color Doppler Ultrasound was performed and described normal renal arteries (left renal artery diameter 3.9mm, right renal artery

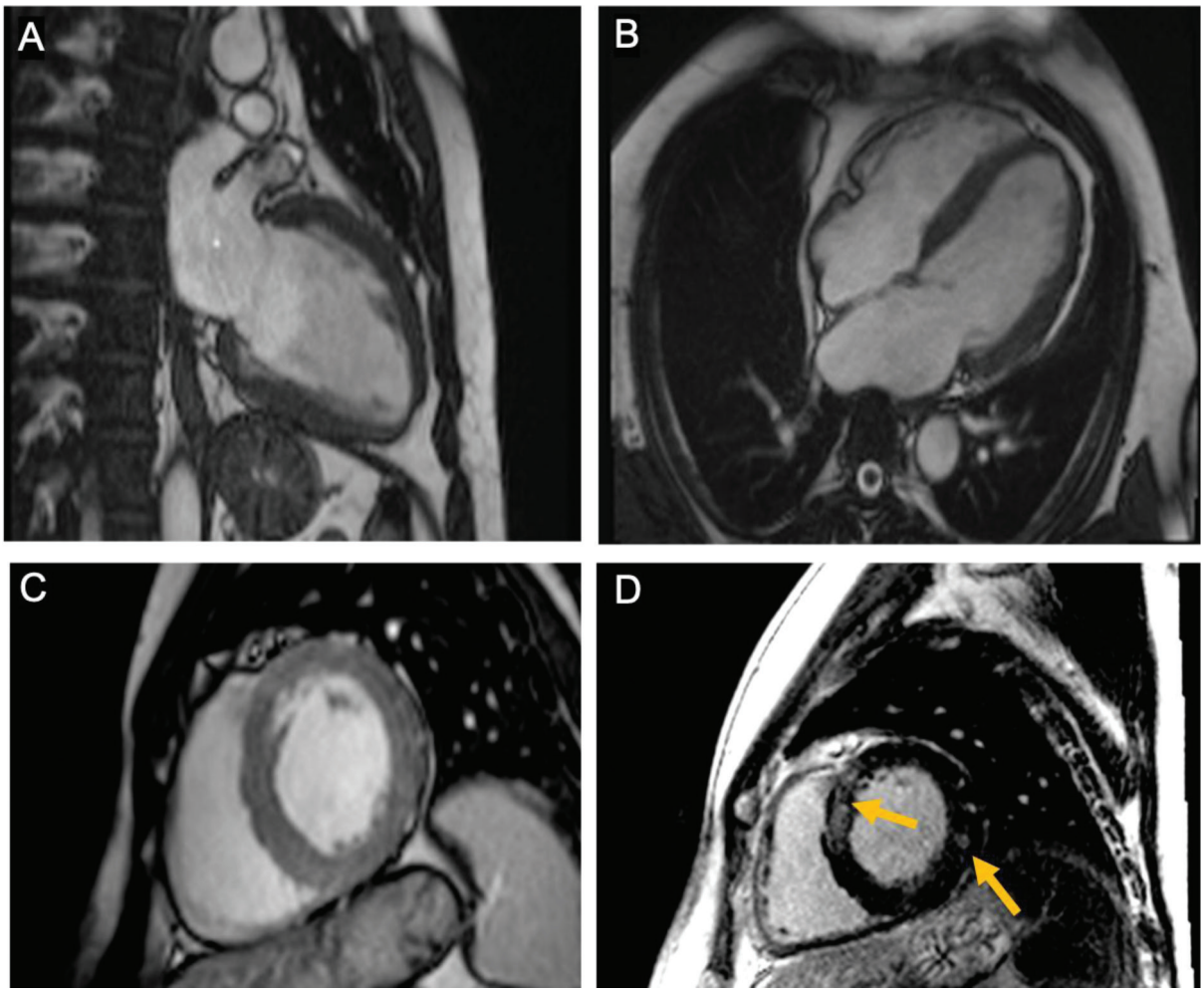

Figure 1. Cardiovascular magnetic resonance imaging. Native cine images (balanced SSFP) in 2 chambers **(A)**, 4 chambers **(B)** and short axis **(C)** views. The left ventricular were hypertrophied but were contracting normally and the systolic function was normal. **D.** Late Gadolinium enhancement sequence in a basal short axis view showing multiple mid-myocardial focal scars in the basal segments of the lateral and anteroseptal walls (yellow arrows).

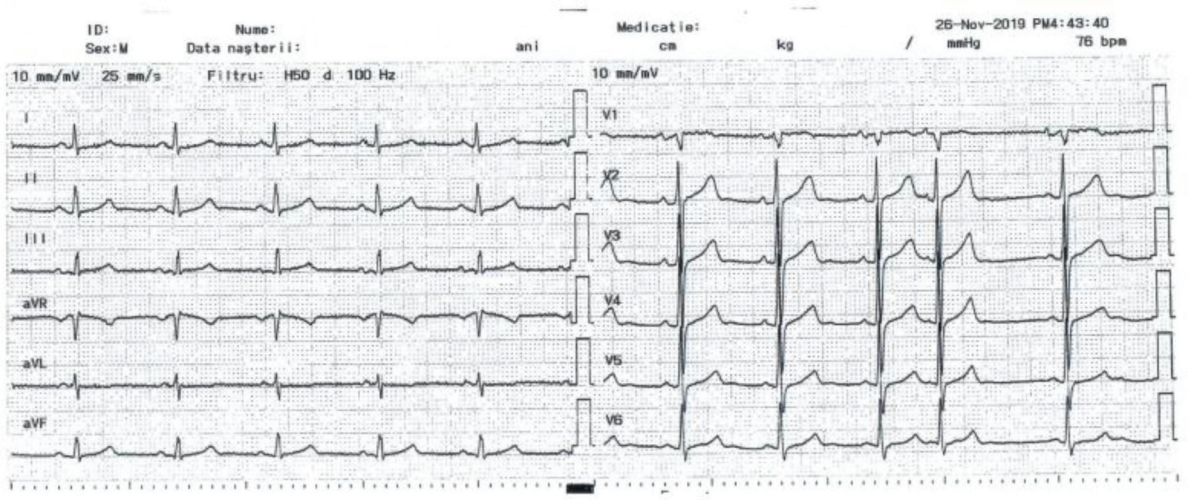

Figure 2. Electrocardiogram obtained after direct current electrical cardioversion. Sinus rhythm with 1 supraventricular extrasystole, voltage criteria for left ventricular hypertrophy but normal morphology of the ST segment and T wave.

4.7mm) with normal kidneys diameter (left kidney 10/4.5mm; right kidney 12/5mm)

A CT scan of the abdomen and pelvis with contrast showed normal adrenal glands without any structural diffuse changes or tumoral masses.

Endocrinological blood tests showed serum aldosterone and renin levels of 98 ng/dL and 0.18 ng/mL/hour, respectively, and cortisol level of 11.5 Ag/dL. The aldosterone/renin ratio was calculated to be 540 ng/dL per ng/(mL/hour).

A diagnostic of arterial hypertension stage 3 and persistent atrial fibrillation was established, and primary hyperaldosteronism was considered the most probably etiology of the resistant increased blood pressure values.

Consequently, both non-pharmacological and pharmacological treatment was initiated. Lifestyle changes were explained to the patient (salt restriction <5g salt/day, alcohol consumption restriction<14units/week, body weight control BMI<30kg/mp, regular aerobic exercise, smoking cessation, a healthy food). The previous medication was stopped, and a new pharmacological treatment was initiated including mineralocorticoid receptor antagonist (50mg spironolactone). In addition, the combination Olmesartan/Amlodipine was introduced for a better control of his blood pressure.

Also, the patient associated atrial fibrillation, with heart rate response about 100/minute. One of the primary goals in this situation was to restore the sinus rhythm. Thus, a transesophageal echocardiography was performed which excluded left atrial appendage thrombus. Consequently, sinus rhythm was restored with direct electric conversion (figure 2). Taking into consideration atrial fibrillation, the treatment of patient included also amiodarone for rhythm control and Apixaban 5mg bid for stroke prevention (CHA2DS2-VASC2 Score =2).

At 3 months follow up, the patient was asymptomatic, with a good tolerance of treatment, with controlled blood pressure 120/80 mmHg under spironolactone treatment, after progressive discontinuation of all the other antihypertensive medication. Blood tests showed that the potassium level was under control.

Discussions

We present the case of a young patient who was admitted to our department for symptoms of heart failure and increased values of blood pressure despite three antihypertensive drugs.

More than one billion people suffer from hypertension around the world. The prevalence of hypertension depends very much on socio-economic factors that influence the patient life. [1] Inappropriate drug prescription, poor patient adherence to treatment, obesity that can mitigate the effects of antihypertensive drugs contribute to poor control of blood pressure.[2] The prevalence of hypertension rises to 60% of the population above 60 years old. [1] SEPHAR III survey showed a hypertension

prevalence of 45.1% that increases with age in the Romanian population. Despite the fact that 72.2% of the patients were treated properly, only 30% had normal blood pressure values. It is reported a decrease in prevalence of hypertension occurring in the same time with an increase control of BP, explained by the improved adherence to the treatment.[3] Framingham Heart Study showed that hypertension incidence increase from 4% at ages 50 to 59 years to 6.2% at ages 70 to 79 years in men, and from 4% at ages 50 to 59 years to 8.6% at ages 70 to 79 years in women. [2]

Hypertension is a chronic disease and also a risk factor for cardiovascular, cerebrovascular and renal diseases, the major causes of morbidity and mortality. The aim of treating hypertension is preventing and attenuating its complications.

Hypertension does not have a specific cause in 90% of the cases. It is called essential hypertension when the etiology cannot be determined. About 10% of patients with hypertension have a secondary cause. Secondary hypertension is more common a resistant hypertension with persisting values over 140/90mmHg despite three antihypertensive drugs, from different classes, including a diuretic, with clinical signs or symptoms suggesting a secondary cause.[5]

Taking into consideration that our patient was young, with increased values of blood pressure and a thicker interventricular septum (12mm), we were looking for a secondary cause (Table 1).

Dissecting the etiology of Hypertension

Etiology of secondary hypertension

As the patient associated hypokalemia, we raised the suspicion of hyperaldosteronism to be the cause of hypertension in his case. The Endocrine Society [6] and the Hypertension Canada's 2016 Guidelines [7] recommend aldosterone screening for some specific presentations such as those presented in Table 2.

Hyperaldosteronism is one of the endocrinological causes of secondary hypertension. Primary hyperaldosteronism is.the most common cause of reversible hypertension. It can be found in 5 to 18% of hypertensive patients. Seventy years ago, Conn described this syndrome in a patient with resistant hypertension and hypokalemia. Approximately 60% of the patients with primary hyperaldosteronism have bilateral idiopathic hyperplasia and 30% have unilateral aldosterone producing adenoma (adrenocortical carcinoma, familial hyperaldosteronism, aldosterone producing adenoma).[8]

Some studies have linked hyperaldosteronism with left ventricular hypertrophy, vascular stiffness, diabetes and other conditions that affect the quality of patient's life.[7] Many of these effects can be reversible when the aldosterone level is controlled. Aldosterone is secreted in glomerulosa zone of adrenal cortex primary as a response to the effect of renin and angiotensin II. It is a retaining salt hormone that via aldosterone receptor facilitates sodium reabsorption, which is the primary mechanism that increase blood pressure. Also, aldosterone is involved in potassium and hydrogen secretion in principal cells of the distal and collecting duct. Hypokalemia can be present in less than 20% cases, in majority of cases being connected with adrenal adenoma.

Aldosterone can directly affect the vessels and the heart inducing fibrosis, endothelial dysfunction and hypertrophy. Some studies suggest that obesity, via adipose cells that secrete some ligands inductors of aldosterone synthesis and secretion can induce hyperaldosteronism and hypertension. [7]

Diagnosing hyperaldosteronism

When suspicion of primary hyperaldosteronism is high, the first step is to obtain a morning plasma aldosterone and renin activity and calculate the ratio between them. If the ratio is higher than 20 to 1 for aldosterone level, the excess of aldosterone is most probably produced by adrenal glands that overrates their production. The test should be performed after correction of hypokalemia, free sodium intake and without any diuretic drugs that can influence the secretion of potassium or sodium.[6]

Also, some confirmatory tests should be performed. These tests are oral sodium loading test, the saline infusion test, fludrohydrocortisone secretion test, captopril challenge test. The clinician choose one of these tests according to the level of hypertension, cardiac condition, renal status, patient compliance (oral sodium loading test and saline infusion test should be avoided in heart failure, severe hypertension or renal failure).[8]

After the diagnose of primary hyperaldosteronism is confirmed, a computer tomography scan

Table 1. Secondary causes of arterial hypertension

Renal causes	*Renal parenchymal diseases*	chronic kidney disease
		polycystic kidney disease
	Renovascular disease	renovascular ischemia
		renal artery stenosis
		fibromuscular dysplasia
Endocrine causes	*Primary aldosteronism*	
	Cushing Syndrome	
	Pheochromocytoma	
	Hyper/hypothyroidism	
	Hyperparathyroidism	
	Congenital adrenal hyperplasia	
Vascular	Coarctation of the aorta	
Medication	*Anti-depressants*	monoamine oxidase inhibitors
		tricyclic antidepressants
	Antipsychotics	Clozapine
		Olanzapine
	Non-steroidal anti-inflammatory drugs	Aspirin
		Acetaminophen
	Sodium containing antacids	
	Systemic corticosteroids	Prednisone
		Dexamethasone
	Appetite suppressants	
	Mineralocorticoids	Fludrocortisone
		ketoconazole
	Immunosuppressants	cyclosporine
	Erythropoietin	
	Estrogen	
	Androgens	
	Oral contraceptives	
	Decongestants	
Others	*Obstructive sleep apnea*	
	Pregnancy	
	Scleroderma	

Table 2. Specific presentations recommending hyperaldosteronism screening

The Endocrine Society	Hypertension Canada's 2016 Guidelines
• *resistant hypertension on triple drug therapy and hypokalemia*	• *resistant hypertension on triple drug therapy, one of which is a thiazide/ thiazide like diuretic*
• *hypertension and adrenal incidentaloma*	• *Hypertension with hypokalemia induced by a thiazide/thiazide like diuretic hypertension and spontaneous hypokalemia*
• *primary hyperaldosteronism in first degree relatives/ family history of early onset stroke*	• *hypertension with adrenal mass*

should be performed to exclude any adrenal carcinoma that may change the clinical strategy. [6]

In our case the serum level of aldosterone and renin were detected and the ratio between them showed a hypersecretion of aldosterone. An abdominal CT scan was performed and excluded an adrenal mass or another morphological causes that could emerge to hyperaldosteronism (renovascular causes, renin producing tumors, etc). Consequently, the final diagnostic was idiopathic primary hyperaldosteronism.

Treatment

Administration of mineralocorticoid receptor antagonists and adrenalectomy represent the major solutions for reducing blood pressure in these patients. In many cases, to obtain a normal blood pressure level, it is necessary to use more antihypertensive drugs. Moreover, with a complete treatment it is also important to minimize the impact of elevated aldosterone on organ damage, to prevent and to correct its organ complications. Some mutations in rectifying potassium channel, alpha-subunit of Na^+/K^+ ATPase (ATP1A1) , Ca^{2+} ATPase calcium channel (ATP2B3) , in voltage-gated calcium channel (CACNA1D) were demonstrated to result in severe aldosterone overproduction, more cardiovascular and renal complications with lower response to the treatment. [9]

Spironolactone is the prototypic mineralocorticoid receptor antagonist, a synthetic drug derived from progesterone. It acts as a progesterone receptor agonist and an androgen antagonist. A second generation of mineralocorticoid receptor antagonists is Eplerenone, much more selective, but more expensive. Spironolactone is used at low doses (12.5-25mg) to minimize the side effects.[9]

A recent study showed that spironolactone is more effective than eplerenone in reducing twice the value of blood pressure due to the facts that spironolactone has a biologically active metabolite whereas eplerenone has an inactive one. Spironolactone has a long half life whereas eplerenone has a short one (about 4 hours).[10]

Even if the blood pressure is normalized and the serum potassium level is normal, it is not known whether all the mineralocorticoid receptors, from the heart, brain, kidney, vasculature are well antagonized, because large prospective studies showed that among the patients with primary hyperaldosteronism treated medically or surgically, the ones treated medically have a higher cardiovascular risks than the others. Also, some studies showed evidences of glucose tolerance deterioration on patients medically treated. [11]

Studies results and meta-analyses showed that adrenalectomy is not entirely curative, and the medical treatment is needed in many of the cases. Thus, it is important to preoperatively predict the possible benefits of the surgery. The predictor factors are age, gender, body mass index, duration of hypertension, family history of hypertension, preoperative number of antihypertensive agents and others. [12] Embase, Cochrane, China National Knowledge Internet (CNKI

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The patient received Spironolactone 50mg od and Olmesartan/Amlodipine 40/5mg od, having a good outcome regarding blood pressure control.

Natural history and prognostic

Various studies showed that primary aldosteronism was associated with a higher incidence of stroke, myocardial infarction, arrhythmias than the

hypertensive patients without primary hyperaldosteronism. Thus, hyperaldosteronism has additional cardiovascular effects independent of blood pressure values and contributes to the organ damage and cardiovascular risks of hypertensive patients (myocardial infarction, stroke, heart failure, kidney disease, diabetes, etc).[13]

On follow up, our patient was asymptomatic, without any sign of congestive heart failure; with controlled blood pressure, in sinus rhythm; he was following the medical recommendations very carefully with salt restriction, regular physical exercises and taking the medical treatment daily.

Conclusion

Hypertension is a common condition which can increase the risk of cardiovascular events, cerebrovascular and renal diseases, the major causes of morbidity and mortality and can severely impair the quality of life. It is very important to look for possible causes that can lead to increased values of blood pressure and not to accept easily the diagnostic of essential hypertension. Detecting the cause and having a proper management of the disease may be the key for improving patient symptoms.

Conflict of interests

There is no conflict of interest to declare.

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