CASE PRESENTATION

Resistant hypertension - still a diagnostic and therapeutic challenge

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Abstract: Objective – Arterial hypertension is an important cardiovascular risk factor with destructive effects on the cardio-renal axis. Approximately 10% of the hypertensive population suffers from the secondary form of this pathology. **Methods –** We hereby present the case of a 47-year-old patient who was addressed to our clinic because of persistent high blood pressure values, despite medication compliance. **Results –** Laboratory findings revealed elevated creatinine and hypokalaemia. Transthoracic echocardiography revealed left ventricular hypertrophy, diastolic dysfunction and subclinical systolic dysfunction. The renal angiogram was normal. The aldosterone: renin ratio was elevated. The tomographic computer exam revealed the presence of two micronodules in the right adrenal gland. The diagnosis of primary hyperaldosteronism was established. After the association of an antialdosteronic agent, a better control of the tensional values was obtained. The patient was referred for the surgical treatment of the lesion. **Conclusions –** Primary hyperaldosteronism accounts for 5-10% of resistant hypertension cases, and unilateral adrenal adenomas are the second most common cause after bilateral idiopathic hyperplasia. When untreated, it is associated with an increased rate of arrhythmias, coronary artery disease, heart failure, stroke, proteinuria and renal dysfunction. The gold standard for the treatment of unilateral adenomas is surgical resection.
Keywords: secondary hypertension, hyperaldosteronism.

Rezumat: Obiectiv – Hipertensiunea arterială, important factor de risc cardiovascular cu efecte distructive pe axa cardiorenală, continuă să reprezinte o provocare diagnostică și terapeutică. Aproximativ 10% din populația hipertensivă suferă de forma secundară a acestei patologii. **Metodă –** Prezentăm cazul unui pacient de 47 de ani care a fost adresat clinicii noastre în contextul valorilor tensionale crescute, în pofida complianței la tratament maximal. **Rezultate –** Biologic s-au decelat sindrom de retenție azotată și hipokaliemie. Ecocardiografia transtoracică a evidențiat hipertrofie de ventricul stâng, disfuncție diastolică și disfuncție sistolică subclinică. Arterele renale au fost normale angiografic. Raportul aldosteron/renină a fost crescut. Examenul computer tomografic a evidențiat micronoduli la nivelul glandei suprarenale drepte. Explorările au stabilit diagnosticul de hiperaldosteronism primar. După asocierea la tratamentul antihipertensiv a antialdosteronicului s-a obținut un control mai bun al valorilor tensionale. Pacientul a fost direcționat pentru cura chirurgicală a leziunii. **Concluzii –** Hiperaldosteronismul primar constituie 5-10% din cazurile de hipertensiune arterială rezistentă, iar adenoamele suprarenaliene unilaterale sunt a doua cea mai frecventă cauză, după hiperplazia bilaterală idiopatică. Netratat, asociază o rată crescută de aritmii, boală coronariană, insuficiență cardiacă, accident vascular cerebral, proteinurie și disfuncție renală. Tratamentul standard recomandat în situația adenoamelor unilaterale este reprezentat de rezecția chirurgicală.
Cuvinte cheie: hipertensiune arterială secundară, hiperaldosteronism.

INTRODUCTION

Arterial hypertension is an important cardiovascular risk factor with destructive effects on the cardio-renal axis. Approximately 10% of the hypertensive population suffers from the secondary form of this pathology[1]. The identification of the secondary causes of hypertension is important, as they may be curable. Furthermore, when left undiagnosed, secondary hypertension can lead to cardiovascular and renal complications, with an increased mortality and burden on the healthcare system.

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CASE PRESENTATION

A 47-year-old patient presented with persistent high blood pressure values, in spite of good compliance with maximal medical therapy. His medical history revealed a recent ischemic stroke with right-sided hemiparesis and arterial hypertension diagnosed 7 years ago.

At admission, the clinical examination revealed no pathological signs, except for a motor deficit on the upper and lower right limbs. The blood pressure was 210/110 mmHg and the heart rate was 65 beats per minute. Resting ECG showed sinus rhythm and left ventricular hypertrophy (LV) with left ventricular strain (Figure 1).

Laboratory findings at admission revealed hypokalemia (K= 3.2 mmol/L) and renal impairment with an estimated glomerular filtration rate (eGFR) of 51.3 mL/min/1.73 m^2. Transthoracic echocardiography showed left ventricular hypertrophy, with LV ejection fraction within normal limits, with longitudinal systolic LV dysfunction and LV diastolic dysfunction with increased filling pressures (Figure 2). The 24-hour blood pressure (BP) monitoring revealed a mean BP of 187/102 mmHg with a maximum BP of 217 mmHg, a minimum systolic BP of 138 mmHg and a non-dipper profile.

When discussing the causes of resistant hypertension, after excluding the pseudo-resistant situations as poor adherence to medical therapy and white-coat phenomenon, the following forms of secondary hypertension were taken into consideration: renovascular disease, renal parenchymal hypertension and endocrine causes. Obesity, excessive alcohol consumption, high sodium intake and obstructive sleep apnoea were too considered, and for the latter the patient was directed to polysomnography at discharge.

For establishing the existence of a renovascular disease, an abdominal ultrasound with colour Doppler of the renal arteries was performed. The renal arteries could not be evaluated because of poor acoustic window (abdominal obesity), but the abdominal ultrasound showed an asymmetry of approximately 15 mm between the kidneys: right kidney 85/40 mm, left kidney 102/56 mm. Therefore, a renal angiography was performed, which excluded the presence of significant stenosis on the renal arteries. The patient had no history of urinary tract infections, the urinalysis was normal and there were no signs of vesicoureteral reflux or other causes of urinary tract obstruction, thus a chronic pyelonephritis was improbable. The laboratory tests were negative for phaeochromocytoma, Cushing's syndrome, thyroid disease and hyperparathyroidism. Plasma aldosterone and renin, and

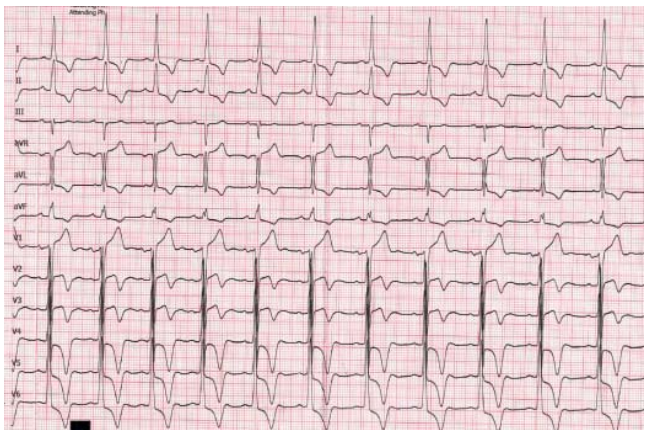

Figure 1. Resting ECG: sinus rhythm 60 beats per minute, left ventricular hypertrophy with left ventricular strain.

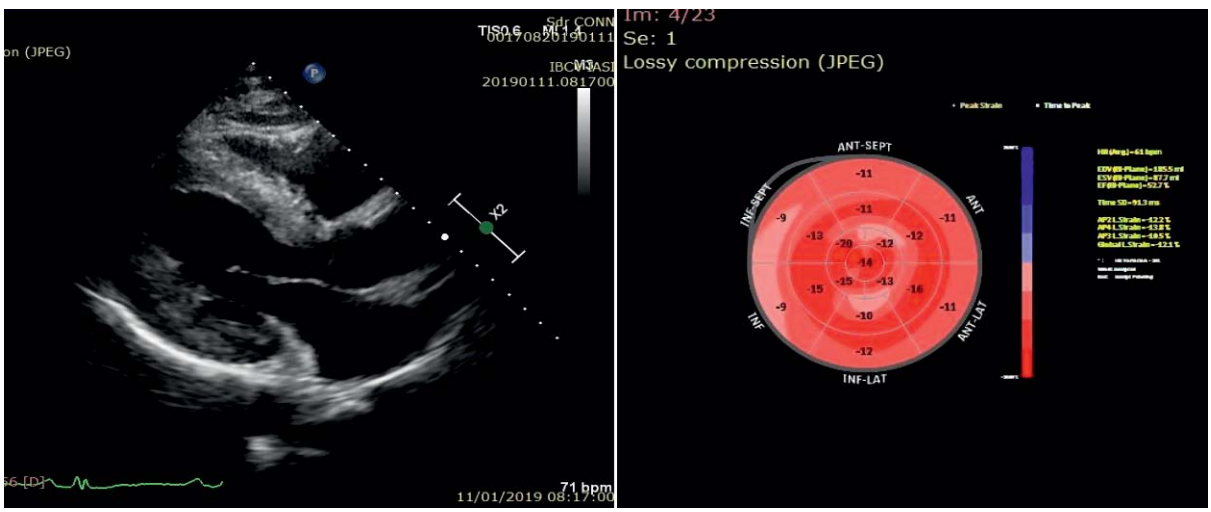

Figure 2. Transthoracic echocardiography, left: parasternal long axis view, LV hypertrophy; right: speckle tracking-longitudinal LV systolic dysfunction.

aldosterone: renin ratio values were as follows: renin =14.4 ng/L, aldosterone 797 ng/L, aldosterone: renin ratio=55.3. The adrenal computed tomography (CT) showed two small nodules on the right adrenal gland (Figure 3).

The abovementioned results were consistent with the diagnosis of primary hyperaldosteronism. After the inclusion of an antialdosteronic drug in high dose in the antihypertensive regimen, the 24-hour BP monitoring revealed a mean BP of 152/91 mmHg, with a maximum systolic BP of 179 mmHg and a minimum systolic BP of 123 mmHg. The patient was referred to surgery for the laparoscopic excision of the right adrenal gland. The diagnosis of adrenal adenoma was confirmed by the anatomopathological examination. After surgery, an optimal control of the blood pressure values was obtained under treatment with beta-blocker, alpha blocker and calcium channel blocker.

DISCUSSION

In 1955, J.W.Conn described for the first time the primary aldosteronism (PA) as a syndrome characterised by „the presence in the urine of excessive amounts of a sodium-retaining corticoid, severe hypokaelmia, hypernatremia, alkalosis, and a renal tubular defect in the reabsorption of water". PA can also present with normokalemia, in which case the hypertension can be misdiagnosed as essential hypertension (EH)[2]. Different studies have reported a prevalence of PA about 5-10% of hypertensive patients[3]. The prevalence of PA increases with the severity of hypertension and patients with PA display more frequently target organ damage (LV hypertrophy, microalbuminuria) and cardiovascular events, with an increased mortality[4,5].

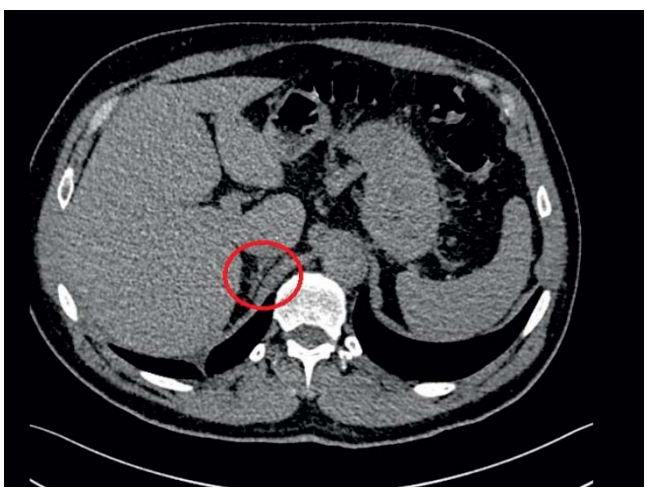

Figure 3. Right adrenal nodules.

Moreover, in a study which included 553 patients, the prevalence of cardiovascular events was significantly higher in PA patients with hypokalemia[6]. When compared to patients with EH, PA patients have greater deterioration of LV diastolic function and a higher prevalence of eccentric hypertrophy[7]. Furthermore, PA patients have greater subclinical systolic dysfunction than EH patients[8].

For the diagnosis of PA, the *European Society of Endocrinology* recommends screening in high risk population, by measuring the plasma aldosterone and renin values and aldosterone: renin ratio. The next step is represented by confirmatory testing (saline loading, fludrocortisone or captopril challenge) which is considered mandatory, with an exception represented by PA cases presenting with spontaneous hypokalemia and a plasmatic aldosterone >200ng/L. CT scanning or magnetic resonance imaging are recommended for the subtype differentiation of PA, but the adrenal vein sampling is recommended in candidates for surgery, as it has greater specificity in differentiating unilateral from bilateral PA[9]. However, the SPARTACUS trial showed that treating PA patients based on CT scanning was non-inferior in terms of antihypertensive treatment intensity and blood pressure control and even superior in terms of associated financial costs[10].

The gold standard for the treatment of unilateral PA is represented by adrenalectomy (9), but unfortunately not all the patients are cured after the surgical intervention. A recent meta-analysis which included 37.763 patients reported a mean hypertension cure rate after unilateral adrenalectomy in PA patients of 50.6%[11].

The presented case illustrates the aspects discussed above and is particular because of the late diagnosis of PA, after 7 years of evolving uncontrolled hypertension, in a patient with established organ damage (stroke, renal impairment). The chronic exposure to high aldosterone levels leads to myocardial and vascular fibrosis, endothelial dysfunction and microangiopathy and can explain the necessity of continuing the antihypertensive therapy post adrenalectomy.

CONCLUSIONS

Although potentially curable, PA continues to be an underdiagnosed disease. Its diagnosis is important and screening in high risk populations should be performed, because when PA remains undiagnosed it associates an increased rate of arrhythmias, coronary artery disease, heart failure, stroke, proteinuria and renal

dysfunction. The gold standard for the treatment of unilateral adenomas is represented by surgical resection.

Conflict of interest: none declared.

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