Endocrine Hypertension – a Multifaceted Disease

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Abstract
Secondary hypertension with an endocrine-associated condition—pheochromocytoma, primary aldosteronism (PA), Cushing's syndrome, acromegaly, congenital adrenal hyperplasia, hypo- and hyperthyroidism, renin-secreting tumors, and hyperparathyroidism—represents a small but heterogeneous group of potentially reversible forms of hypertension. High clinical suspicion is the cornerstone of diagnosing these different patterns of often severe and refractory hypertension.
We report a series of 3 cases of endocrine secondary hypertension with particular clinical presentations and paraclinical findings in which the accurate diagnosis led to successful treatment of high blood pressure.

Keywords
secondary hypertension, primary aldosteronism, pheochromocytoma, Addison's disease

Rezumat
Hipertensiunea arterială secundară de cauză endocrină - feocromocitomul, aldosteronismul primar (AP), sindromul Cushing, acromegalia, hiperplazia congenitală a glandelor suprarenale, hipo- și hipertiroidia, tumorile secretante de renină și hiperparatiroidismul - reprezintă un grup mic, dar heterogen de forme potențial reversibile de hipertensiune arterială. Suspiciunea clinică ridicată este piatra de temelie a diagnosticului acestor diferite modele de hipertensiune uneori severă și refractară.
Raportăm o serie de 3 cazuri de hipertensiune secundară de cauză endocrină cu prezentare clinică și constatări paraclinice particulare, în care diagnosticul precis a dus la un tratament de succes al hipertensiunii arteriale.

Cuvinte cheie
hipertensiune arterială secundară, aldosteronism primar, feocromocitom, boala Addison

Introduction

Hypertension has been recognized for a long time as a major cardiovascular risk factor. In most cases, hypertension is primary (essential or idiopathic), but there is also a small group of approximately 10% that present a secondary form. Secondary hypertension is usually caused by a potentially reversible cause (renal, vascular, or endocrine), and its identification and proper treatment can lead to normal blood pressure (BP) values. The secondary forms are very easily missed in clinical practice, therefore clue elements for diagnostic guidance are needed: age below 30 years at onset, absence of family history for hypertension, overweight, and unexpected evolution in patients with previously well-controlled values [1,2].

The endocrine conditions associated with secondary hypertension are pheochromocytoma, primary aldosteronism (PA), Cushing's syndrome, acromegaly, congenital adrenal hyperplasia, hypo- and hyperthyroidism, renin-secreting tumors, and hyperparathyroidism. Although there is no data to support routine screening for endocrine causes, it is essential to keep a high clinical suspicion based on the clinical elements and presentation of these forms. PA represents the majority of these cases with a prevalence ranging from 4.6% to 13% in patients with hypertension and up to 20% in refractory cases [2,3].

In PA, the typical findings are low levels of plasma renin and high plasma levels of aldosterone with negative consequences on the arterial wall, heart, and kidneys. PA is rarely identified simply because it mimics essential hypertension [4].

Phaeochromocytoma is a neuroendocrine tumor secreting high amounts of catecholamines, with a wide variety of clinical presentations ranging from no symptoms at all to sudden death [4].

Even though the clinical profile of Addison's disease is characterized by hypotension, an imbalance in its treatment may sometimes lead to hypertension instead.

Presentation of Case Series

1. Case I

A 56-year-old male with a history of more than 20 years of hypertension was admitted to our clinic for uncontrolled BP values, despite maximal medical treatment according to the current guidelines. He was known to have sleep apnea for 10 years, and he had recently undergone a magnetic resonance imagistic exam (MRI) that ruled out renal artery stenosis. He reported the following side effects from different medications: edema at amlodipine, cough at angiotensin-converting enzyme inhibitors (ACEI), and gynecomastia

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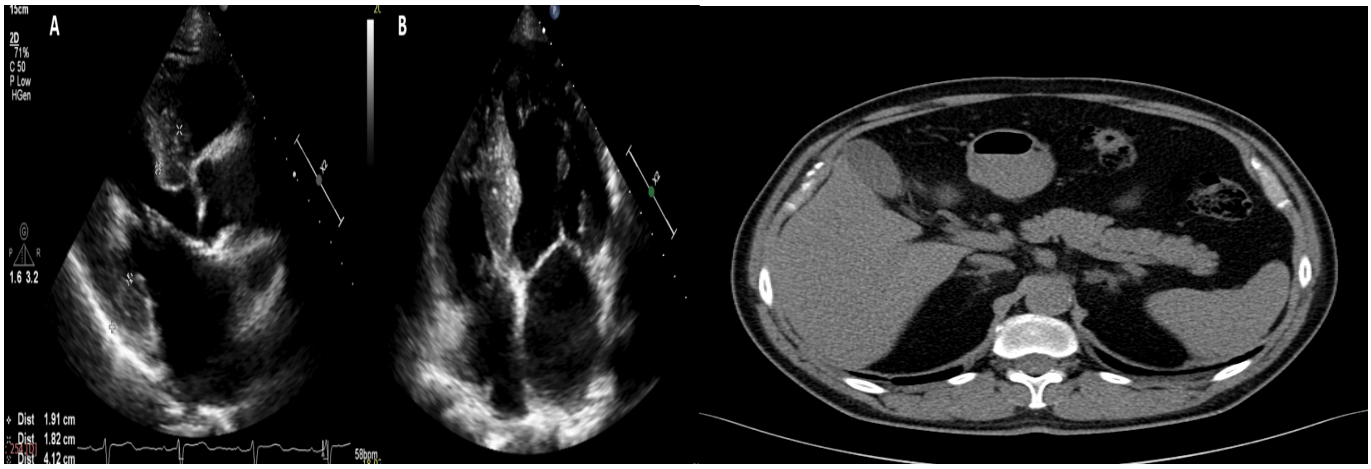


Figure 1 - Left-Transthoracic echocardiography parasternal long axis view: LVH, left atrial enlargement. Right-Abdominal CT: left adrenal nodule of 10x10x9 mm.

at spironolactone. Upon admission, the BP was 162/99 mmHg, with a grade II apical systolic murmur, a heart rate of 62 bpm, and normal pulmonary auscultation. The electrocardiogram documented sinus rhythm, a left anterior fascicular block, left ventricular hypertrophy (LVH), and 2 premature ventricular contractions. The biological workup showed hypercholesterolemia (total cholesterol = 230 mg/dl), hypokalemia (K = 3,2 mmol/l), and renal dysfunction (eGFR = 64 ml/min/1,73 m^2). The echocardiography showed preserved ejection fraction with an important LVH, left atrial enlargement, and mild mitral and aortic regurgitations (Figure 1). The ambulatory blood pressure monitoring (ABPM) confirmed the uncontrolled BP values with a mean value of 176/88 mmHg. The coronary angiography excluded any atheromatous lesions. Given the uncontrolled BP, a computer tomography (CT) exam was performed and indicated the presence of a left adrenal nodule (10x10x9 mm), suggestive of PA. For confirmation, the aldosterone/plasmatic renin ratio was measured. In our case, the report was high (10,2) with an increased aldosterone level of 250 ng/L which confirmed our suspicion. The patient was referred for adrenalectomy. Three months after the intervention, the patient had controlled BP with a mean value of 128/73 mmHg, under treatment with sartans and beta-blockers.

2. Case 2

A 62-year-old female patient was admitted to our clinic for chest pain accompanied by headache, palpitations, and increased sweating. She was diagnosed 10 years ago with type 2 diabetes mellitus and grade 3 arterial hypertension. On admission, the patient had a BP of 200/100 mmHg, with grade II cardiac murmur in the mitral position, and a heart rate of 120 beats per minute, without pulmonary signs of congestion. The electrocardiogram documented sinus rhythm, Q wave in DI, DII, DIII, and aVL, with ST-segment elevation in V_2–V_5 (2-3 mm), and negative T waves in aVL, DI. The biological workup showed elevated cardiac enzymes (CK-MB = 40 U/l, TGO = 87 U/l, LDH = 675 U/l), hyperglycemia, and renal dysfunction (eGFR = 34 ml/min/1,73 m^2). The echocardiographic exam revealed moderate LVH and moderate hypokinesia of the 1/3 apical interventricular sept, apex, and anterior wall with a reduced ejection fraction (40%). The coronary angiography revealed normal coronary arteries. As the patient's condition evolved, the patient became hemodynamically unstable with high BP value variations (SBP between 40 mmHg and 220 mmHg). The worsening of the evolution required supplementary investigations. Therefore, an abdominal echography exam followed by a CT was performed. These evaluations depicted a right suprarenal lesion (63/59/56 mm) with central necrosis and uneven contrast media, suggestive of pheochromocytoma (Figure 2). For confirmation, urinary and plasmatic metanephrines were measured, and both of them were increased. Soon after clinical stabilization with alpha- and beta-blockers, the patient underwent surgery (right adrenalectomy) with excellent results in evolution.

3. Case 3

A 75-year-old diabetic woman who had been living with Addison's disease for four decades (last adrenal crisis at the age of 64), currently under hormone replacement therapy, was admitted to the emergency department because of retrosternal chest pain related to exertion. Antianginal medication relieved this pain, which started a month ago and increased in the last week. The physical examination result was normal besides overweight (BMI = 27 kg/m^2) and high BP (170/100 mmHg). The electrocardiogram was normal. Notable laboratory findings on presentation included hypokalemia (K = 3,3 mmol/L) and increased levels of troponin (hs-cTnI = 174 ng/L). Echocardiography showed normal global and segmental systolic function of the left ventricle with preserved ejection fraction (60%), normal diastolic function, mild degenerative mitral regurgitation, and mild tricuspid regurgitation. Coronary angiography revealed a sub-occlusion of the left main and 80% stenosis of the left anterior interventricular artery with hypoplasia. Therefore, a percutaneous coronary intervention was realized by implanting a drug-eluting stent at the level of the left main and yielded excellent results. Considering the high BP values, an ABPM was performed which revealed a dipper pattern and newly onset increased BP, particularly diurnal (maximum SBP = 233 mmHg). The patient underwent an endocrine

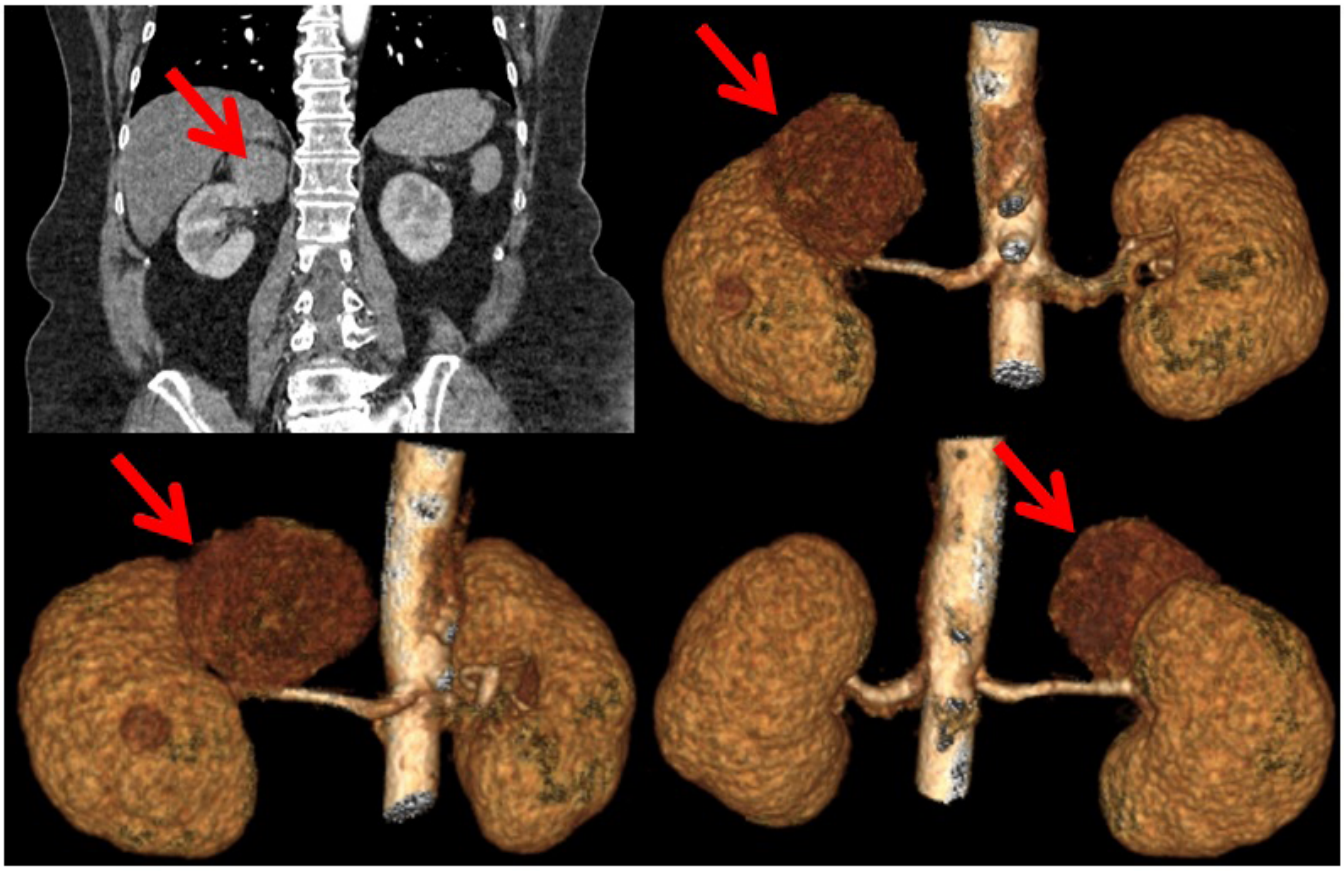


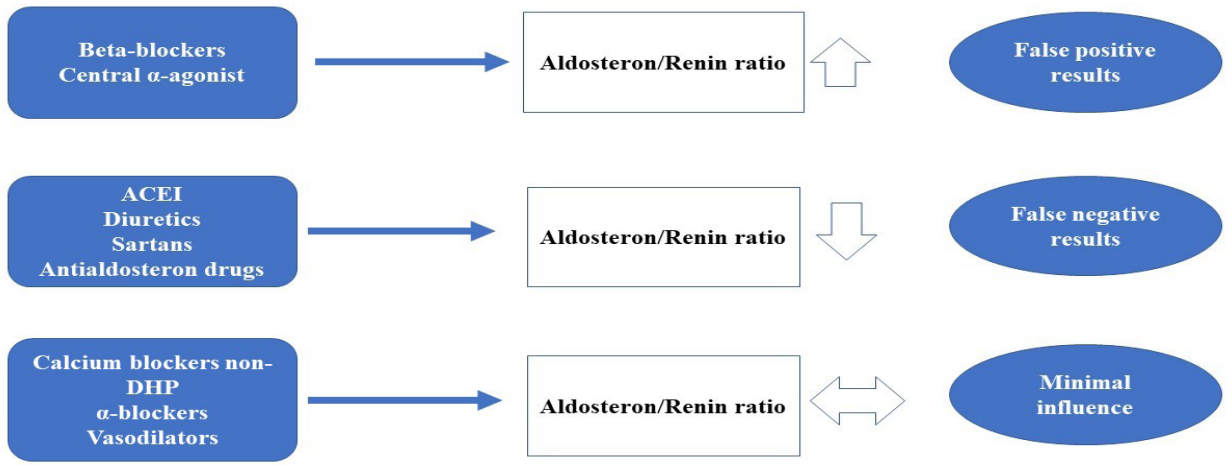
Figure 2 - Abdominal CT: right suprarenal lesion with central necrosis.

evaluation that revealed increased cortisol values which required the adjustment of existing hormonal therapy.

Discussions

The prevalence of PA is directly proportional to the severity of hypertension. Patients with PA have an increased risk of cardiovascular events and frequently present with secondary organ damage such as LVH, diastolic dysfunction, and microalbuminuria. Hypokalemia is a predictive risk factor for major adverse cardiac events. There are several situations in which screening for PA is recommended: moderate to severe hypertension, resistant hypertension, controlled hypertension with 4 different types of antihypertensive drugs, young age at onset, hypertension associated with spontaneous or diuretic-induced hypokalemia, incidentaloma, or sleep apnea. Furthermore, the aldosterone/plasmatic renin ratio requires four weeks of no antihypertensive treatment that affects it (Figure 3). Levels of plasmatic aldosterone >200 ng/L associated with hypokalemia do not require further confirmation, so we did not proceed with extra examinations such as sodium loading over three days or a saline infusion test. Furthermore, CT was used to rule out an adrenal carcinoma and differentiate between distinct subtypes of PA (unilateral suprarenal adenoma vs. bilateral adrenal hyperplasia). MRI was another imaging test that could have been employed, although it showed no superiority in diagnosing disease subtypes. While the gold standard treatment for the unilateral type is adrenalectomy, those with bilateral hyperplasia need treatment with mineralocorticoid antagonists [5,6,7,8,9,10].

First described in 1886 by Felix Frankel, pheochromocytoma is a neuroendocrine tumor that releases catecholamines. In general, its clinical manifestation is represented by the following triad: intense sweating, headache, and palpitations, alongside pallor and paroxysmal hypertension crises that are especially determined by the administration of beta-blockers, tricyclic antidepressants, metoclopramide, or opioids. However, the clinical symptoms are so different that pheochromocytoma can resemble many common illnesses as occurred in our case when the patient presented with acute coronary syndrome (ACS). The activation of alpha- and beta-receptors lead to coronary constriction and positive inotropic and chronotropic effects. Therefore, ACS may be induced by hypoxia as a result of higher cardiac contractility and potential tachyarrhythmias. Besides catecholamines, pheochromocytoma could also release adrenomedullin, opioid peptides, Y neuropeptide, endothelin-1, and corticotropin-releasing factor. The best characterization for pheochromocytoma is reflected by the “10’s rule,” meaning 10% are located bilaterally, 10% are extra-adrenal, 10% are malign, 10% have familial distribution, 10% appear in children, 10% do not associate



ACEI – angiotensin-converting enzyme inhibitors, DHP - dihydropyridines

Figure 3 - Antihypertensive medication influence on the PA screening tests.

hypertension. Even in the presence of normal BP values, screening is recommended for all patients who experience resistant hypertension or with a familial history of pheochromocytoma or suprarenal incidentaloma. The electrocardiographic signs are polymorphic and diffuse negative deep T waves or any other repolarization changes can be identified. The appearance of post-coronary angiography hypertensive paroxysm increased the possibility of pheochromocytoma thus, a careful analysis was performed by abdominal echography and CT, but the ultimate diagnosis was established by the plasmatic and urinary measurement of metanephrines. Sometimes, additional investigations might be required, such as MRI, PET-CT, or SPECT. Importantly, before undergoing adrenalectomy, patients must undergo up to 2 weeks of a preparation regime that consists of alpha- and beta-blocker medication [11,12,13,14,15,16].

In Addison's disease, the ischemic risk is higher, especially in women, and it is directly proportional to the steroid substitution. Although current replacement therapy attempts to match the normal circadian pattern of cortisol, periods of sub- and supraphysiological cortisol concentration occur. Nevertheless, emerging therapies strive to mimic physiological cortisol rhythms, improving the quality of life in these patients. The cortisol excess may lead to overweight, diabetes mellitus, hypertension, or lipid imbalance, all of which are the most common cardiovascular risk factors for atherosclerosis and coronary artery disease. On the other hand, low levels of cortisol will lead to increased inflammatory markers such as interleukin-1, interleukin-6, and tumor necrosis factor α, which are promotors for atherosclerosis and thus generate high BP values. As previously mentioned, when facing sudden onset hypertension in a patient with Addison's disease, one should exclude the possibility of an overdose in glucocorticoid therapy [17,18,19,20].

Conclusions

Endocrine hypertension is indeed a multifaceted disease, and PA and pheochromocytoma carry a significant mortality and morbidity rate if left untreated. At the same time, iatrogenic causes could also generate significant cardiovascular effects, being a silent killer. Biochemical tests and correct interpretation of their results are required to provide a precise diagnosis and optimal management, especially in those who are at high risk. A multidisciplinary team including a cardiologist, an endocrinologist, and a surgeon is the key to success.

Conflicts of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Jun Y, Jimmy S, Peter JF. Diagnosing endocrine hypertension: a practical approach. Nephrol 2017;22(9):663–677.
2. Isabella S, Felix B, Thomas FL. Secondary causes of hypertension. In: Camm AJ, Lüscher TF, Maurer G, Serruys PW, editors. ESC CardioMed. 3rd ed. London: Oxford University Press; 2018;
3. Reena MT, Ewa R, Prapimporn CS, Leonor C, Endocrine hypertension: An overview on the current etiopathogenesis and management options. World J Hypertens 2015;5(2):14–27.
4. William FY, David AC, Jacques WML, Michael S, Stephen CT. Screening for endocrine hypertension: an endocrine society scientific statement. Endocr Rev 2017;38(2):103–22.
5. Er LK, Wu VC. Call for screening for primary aldosteronism: an underdiagnosed and treatable disease, J Thorac Dis 2018;10(2):557–9.
6. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffallo F, et.al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol 2017;69(14):1811–20.
7. Born-Frontsberg E, Reincke M, Rump LC, Lorenz R, Hahner S, Diederich S. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. J Clin Endocrinol Metabol 2009;94(4):1125–30.
8. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et.al. The management of primary aldosteronism: case detection, diagnosis,

and treatment: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol 2016;101(5):L1889–916.

9. Zhou Y, Zhang M, Ke S, Liu L. Hypertension outcomes of adrenalectomy in patients with primary aldosteronism: a systematic review and meta-analysis. BMC Endocr Disord 2017;17(1):61.

10. Kounatiadis P, Petroglou D, Kolettas V, Karvounis H, Primary aldosteronism of late onset: a case report. HIPPOKRATIA 2014;18(2):180–82.

11. Yu R, Furmark L, Wong C, Cardiac abnormalities associated with pheochromocytoma and other adrenal tumors. Endocr Pract 2009;15(1): 10–16.

12. Tsirilin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA, Pheochromocytoma: a review. Maturitas 2014;77(3):229–38.

13. Guerrero MA, Schreinermakers JM, Vriens MR, et al. Clinical spectrum of pheochromocytoma. J Am Coll Surg 2009;209(6):727.

14. Kassim TA, Clarke DD, Mai VQ, et al. Catecholamine-induced cardiomyopathy. Endocr Pract 2008; 14(9):1137–49.

15. Chioncel V, Adam F, Sinescu I, Păun D, Sinescu C. Particularitățile clinice și paraclinice la pacienții hipertensivi cu feocromocitom – studiu retrospectiv. Rom J Cardiol 2012:22(2).

16. Radojkovic D, Stojanovic M, Pesic M, Radojkovic M, Radenkovic S, et al. Clinically “silent” giant pheochromocytoma. case report. Acta Endocrinologica (BUC) 2013;9(1):121–29.

17. Skov J, Sundstrom A, Ludvigsson JF, Kampe O, Bensing S. Sex-specific risk of cardiovascular disease in autoimmune addison disease – a population-based cohort study. J Clin Endocrinol Metab 2019;104(6):2031–40.

18. Rahvar AH, Haas CS, Danneberg S, Harbeck B. Increased cardiovascular risk in patients with adrenal insufficiency: a short review. Biomed Res Int 2017;2017:3691913.

19. Schumacher MM, Larsen TR, Sane DC. Cardiac manifestations of adrenal insufficiency. Rev Cardiovasc Med. 2016;17(3–4):131–36.

20. Henry M, Kevin GFT, Ian LR, Sleep, cognition and cortisol in Addison’s disease: a mechanistic relationship. Front Endocrinol (Lausanne) 2021;12:694046.