

PHEOCHROMOCYTOMA: INTRICATE CARDIOVASCULAR MANIFESTATIONS

Andreea Timofte², Mirela Claudia Nechita⁴, Alexandru-Dan Costache^{1,3}, Silvia Chiriac³, Ovidiu Mitu^{1,2}, Florin Mitu^{1,3}, Voichița Mogoș⁴, Irina-Iuliana Costache^{1,2}

¹University of Medicine and Pharmacy „Gr. T. Popa” Iași, Romania

²Department of Cardiology, Saint Spiridon Emergency County Hospital Iași, Romania

³Department of Cardiovascular Rehabilitation, Clinical Rehabilitation Hospital Iași, Romania

⁴Department of Endocrinology, Saint Spiridon Emergency County Hospital Iași, Romania

Correspondent author: Florin Mitu

Email: mitu.florin@yahoo.com

Rezumat

Prezentăm cazul unei paciente, în vârstă de 60 de ani, dislipidemică, obeză, diabetică și hipertensivă, cu antecedente de feocromocitom suprarenalian drept operat (1999 - fără reevaluare chirurgicală sau endocrinologică ulterioară), care se prezintă pentru valori tensionale crescute și reapariția simptomelor (cefalee, palpitații, transpirații), cu accentuare progresivă în ultimele luni. Pacienta asociază dureri la nivelul lojei renale drepte și scădere ponderală. Examenul clinic a evidențiat eritroză facială, tegumente transpirate, zgomote cardiace tahicardice, valori tensionale crescute și cu tendința la hipotensiune ortostatică. Electrocardiografic se decelează tahicardie sinusală, semne de hipertrofie ventriculară stângă, cu modificări secundare de fază terminală, aspect morfologic confirmat de ecocardiografia transtoracică. Ecografia abdomino-pelvină obiectivează o formațiune tumorală de mari dimensiuni la nivelul glandei suprarenale drepte și un nodul hepatic. În contextul simptomatologiei, se ridică suspiciunea de feocromocitom recidivat, confirmată biochimic prin creșterea normetanefrinelor urinare și imagistic prin examen CT abdomino-pelvin, pacienta având indicație de tratament chirurgical cu viză curativă.

După completarea bilanțului preoperator (monitorizare Holter ECG, monitorizare ambulatorie a tensiunii arteriale), pe perioada spitalizării, s-a ajustat schema antihipertensivă prin asocierea a 4 clase de medicamente antihipertensive, episoadele de hipotensiune ortostatică fiind gestionate prin administrarea de glucocorticoizi și soluții coloidale de repleție volemică.

Pacienta a fost direcționată către clinica de chirurgie generală, în vederea exciziei tumorale, cu respectarea protocolului periprocedural de pregătire antihipertensivă. Cu toate că evoluția postprocedurală a fost favorabilă, pacienta prezintă un risc crescut de recidivă, fiind necesară evaluarea anuală, pe perioadă de 10 ani. De asemenea, din cauza asocierii factorilor de risc cardiovascular și a afectării de organ țintă, pacienta necesită consult cardiologic periodic.

Cuvinte cheie: feocromocitom, hipertensiune arterială secundară, hipotensiune ortostatică, recidivă tumorală, hipertrofie ventriculară stângă.



INTERNAL MEDICINE

Clinical Cases

Abstract

We present the case of a 60-year-old female patient, dyslipidemic, obese, diabetic and hypertensive, with a history of resected right adrenal pheochromocytoma (1999 - no subsequent surgical or endocrinological re-evaluation), presenting for increased blood pressure values and the recurrence of symptoms (headaches, palpitations, sweating), with progressive accentuation in the last months. The patient associates pain in the right costovertebral angle and weight loss. The clinical examination revealed facial erythrosis, excessive sweating, tachycardic heart sounds, increased blood pressure and orthostatic hypotension. Electrocardiography reveals sinus tachycardia, signs of left ventricular hypertrophy, with repolarization abnormalities, morphological aspect confirmed by the transthoracic echocardiography. An ultrasound of the abdomen and pelvis ultrasound objectified a large tumor formation at the level of the right adrenal gland and a liver nodule. In the context of the symptoms, the suspicion of recurrent pheochromocytoma was raised, confirmed biochemically by the increase in urinary normetanephrines and through imagistic methods (CT scan of the abdomen and pelvis), the patient having an indication for curative surgical treatment.

After completing the preoperative assessment (ECG Holter monitor, ABPM), during the hospitalization period, the antihypertensive regimen was adjusted by combining 4 antihypertensive drugs, episodes of orthostatic hypotension being managed by administering glucocorticoids and colloidal solutions for volume repletion.

The patient was referred to the general surgery clinic for resection of the tumor, following the antihypertensive preparation protocol. Although the post-procedural evolution was favorable, the patient presents a high risk of tumor recurrence, requiring annual evaluation for a period of 10 years. Also, due to the association of cardiovascular risk factors and target organ damage, the patient requires periodic cardiological evaluation.

Keywords: *pheochromocytoma, secondary hypertension, orthostatic hypotension, tumor recurrence, left ventricular hypertrophy.*

Introduction

Pheochromocytomas are rare neuroendocrine tumors that originate in chromaffin tissue and by secretion of catecholamines produce variant effects that tend to mislead the physicians to a wrong diagnosis. Patients with neurofibromatosis, von Hippel-Lindau disease, familial pheochromocytoma/ paraganglioma syndrome or multiple endocrine neoplasia syndromes carry a higher risk of developing pheochromocytoma⁽¹⁾.

This tumor excessively produces one or more catecholamines (epinephrine, norepinephrine and dopamine). The consecutive increased activation of the sympathetic nervous system is responsible for the symptomatology. Systemic arterial hypertension is the most common cardiac repercussion and it is particularly suggestive when associated with the clinical triad: headache, sweating and palpitations⁽²⁾.

Hypertension is often paroxysmal, in some patients occurring on a background of sustained hypertension. Some patients also present with unexplained orthostatic hypotension⁽³⁾.

Additionally, patients complain about dizziness, weight loss, nausea and vomiting, abdominal and back pain and pale and moist skin. The excessive secretion of catecholamines may be lethal due to organ failure secondary to severe systemic arterial hypertension or hypertensive crisis. In addition, electrophysiological complications, such as a prolonged QT and ventricular arrhythmias are described. For all these reasons, rapid diagnosis is mandatory.

The diagnosis of pheochromocytoma requires demonstration of the excessive production of catecholamines. Therefore, blood and urinary levels of epinephrine, norepinephrine and their metabolites (metanephrine, normetanephrine) must be determined.

A diagnostic work-up is completed via anatomical imaging with abdominal sonography/ CT scan and magnetic resonance imaging of the kidney and the adrenal lodges. In addition, functional scans, such as I-123 MIBG scintigraphy must be undertaken in order to improve diagnostic specificity and sensitivity and to detect metastases and multifocality.

Surgical treatment of pheochromocytoma via conventional open surgery or laparoscopy provides excellent long-term results in experienced centers.

Peri-operative management is of paramount importance in order to normalize blood pressure and avoid hypertensive crisis and coronary vasospasm that may be elicited by massive catecholamine release during intra-operative tumor manipulation, which can be fatal⁽⁴⁾.

Although they have only about a 10% incidence of malignancy, these tumors are associated with a high risk of morbidity and mortality from cardiovascular complications⁽⁵⁾.

Case presentation

A 60-year old female patient, dyslipidemic, obese, diabetic and hypertensive, with a history of resected right adrenal pheochromocytoma (1999 - with no subsequent reevaluation), is currently presenting with high blood pressure (240/110 mmHg) - with predominantly nocturnal occurrence, intense headaches, profuse sweating (predominantly in the upper half of the body), palpitations, tremors, paresthesia, episodes of facial flushing, pain in the right costovertebral angle and weight loss (10 kg in 6 months). She was a non-smoker, denied chronic alcohol consumption and had chronic treatment previously with ACE inhibitor, calcium channel blocker, thiazide-like diuretic, lipid-lowering



INTERNAL MEDICINE

Clinical Cases

agent and insulin. Clinical examination on admission revealed facial erythrosis, excessive sweating, tachycardic heart sounds (HR =100/min), increased blood pressure (BP =200/100 mmHg) and orthostatic hypotension (BP =175/80 mmHg).

Subsequent paraclinical examinations were conducted. The electrocardiogram showed sinus tachycardia and LVH with repolarization abnormalities (Figure 1).

Laboratory blood and urinary tests revealed impaired kidney function ($\text{eGFR} = 43 \text{ ml/min/1.73 m}^2$), moderate glycemic control ($\text{HbA1c} = 7,7\%$), dyslipidemia ($\text{LDL} = 122 \text{ mg/dl}$), leukocytosis ($\text{WBC} = 14320/\text{mm}^3$), high levels of urinary normetanephrines ($1411 \mu\text{g}/24 \text{ h}$), high levels of urinary cortisol ($299 \mu\text{g}/24 \text{ h}$).

Transthoracic echocardiography revealed normal systolic function of the left ventricle, with an ejection fraction of 65%, diastolic dysfunction grade 1 (impaired relaxation), concentric left ventricular hypertrophy, mild mitral valve regurgitation and mild aortic valve regurgitation (Figure 2).

The findings of the abdominal and pelvic CT scan were: liver with a 48 mm nodular lesion in segment 4B, hypodense, with inhomogeneous contrast uptake (suggestive for a hemangioma; differential diagnosis with a secondary determination); a voluminous tumor formation 72/65/53 mm in the right adrenal gland, well demarcated, with

inhomogeneous and progressive contrast uptake, with hypodense necrotic areas of up to 28 mm (differential diagnosis between a pheochromocytoma and an adrenocortical carcinoma) - the formation compresses and pushes the left renal vein and the IVC anteriorly; left adrenal gland with a tumor formation 38 mm, with adenoma-type contrast outlet; uterus with fibromatous nodules; no pathological abdominal adenopathy (Figure 5).

By the correlation of clinical and paraclinical results we established the final diagnosis as recurrent operated right adrenal pheochromocytoma complicated by secondary hypertension, hypertensive cardiomyopathy, orthostatic hypotension and premature ventricular contractions.

The treatment aimed to improve patient's symptoms and prognosis. The antihypertensive regimen was adjusted by combining: short-acting α_1 blocker, angiotensin II receptor blocker (ARB), $\alpha+\beta$ blocker and a calcium channel blocker, episodes of orthostatic hypotension being managed by administering glucocorticoids and colloidal solutions for volume repletion.

The patient was referred to the general surgery clinic for resection of the tumor, following the preparation protocol: preoperative (alpha adrenergic blockade for the intraoperative prevention of hypertensive crises, followed by beta

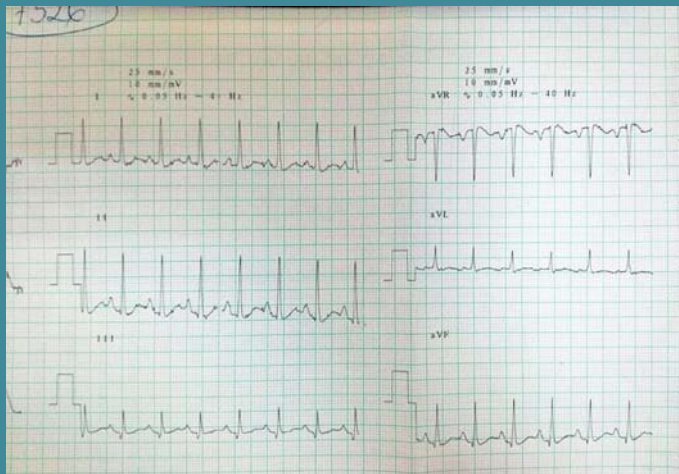
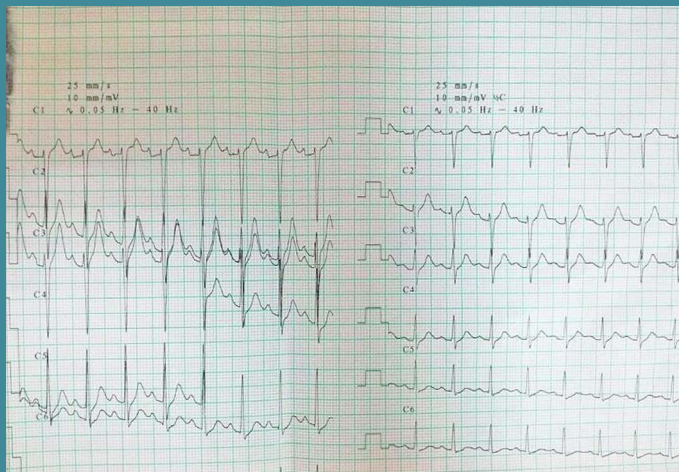


Figure 1.
ECG tracing



Im: 1/1
Se: 0001 4 L 2.7 cm
Lossy compression (JPEG)
2 L 1.6 cm
1 L 4.1 cm

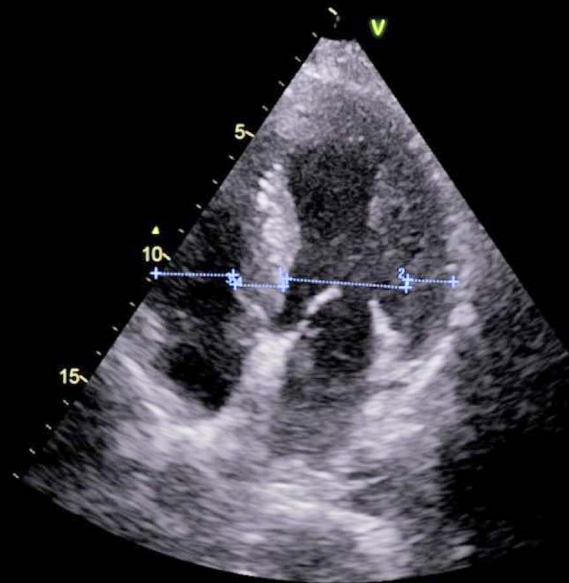


Figure 2.
Echocardiography
- 2D imaging,
Apical 4 chamber
view - left
ventricular
hypertrophy



INTERNAL MEDICINE

Clinical Cases

adrenergic blockade), intraoperative (short-acting antihypertensive medication) and postoperative (volume replacement solutions in large volume), with favorable post-procedural evolution.

Discussion

Pheochromocytoma can produce excessive amounts of catecholamines and release them continuously or intermittently⁽⁶⁻⁷⁾.

Approximately 90% of patients with pheochromocytoma present with sustained or paroxysmal hypertension⁽⁸⁻⁹⁾. Hypertension in pheochromocytoma usually manifests as high peripheral resistance and low heart index.

Epinephrine-secreting pheochromocytoma usually causes patients to experience paroxysmal symptoms, while patients with norepinephrine-secreting tumors usually have persistent symptoms related to the continuous catecholamine overdose⁽¹⁰⁾. In our case, the patient's norepinephrine level was elevated and the patient had a history of hypertension. Nonetheless, in the years following the first resection of the tumor, the patient continued to have high blood pressure. An explanation could be that the patient has a high probability of developing hypertension, due to the association of several risk factors (type 2 diabetes mellitus, obesity and chronic kidney disease). Another aspect to be taken into

consideration is the lack of postoperative follow-up which may have led to an undiagnosed tumor recurrence.

Occasionally, patients with pheochromocytoma experience hypotension or even shock. The pathophysiological factors of hypotension and shock include tumor necrosis leading to a sudden decrease in continuous catecholamine secretion, adrenergic receptor desensitization, and decreased vascular volume⁽¹¹⁾.

In our case, the pheochromocytoma may have been related to the sudden decrease in catecholamine secretion caused by tumor necrosis and the CT scan confirmed an adrenal pheochromocytoma with areas of necrosis. This was also consistent with the ABPM results which showed hypertension paroxysms followed by hypotension. Considering the fact that our patient is diabetic, presenting with paresthesia and orthostatic hypotension, a differential diagnosis should be made with diabetic autonomic neuropathy⁽¹²⁾.

Pheochromocytoma can also cause other cardiovascular complications, including cardiac hypertrophy, heart failure, arrhythmias, ischemic heart disease and even acute myocardial infarction, which are due to the effects of secreted catecholamines⁽¹³⁻¹⁴⁾.

Norepinephrine secreted by pheochromocytoma can cause structural and functional remodeling of the heart, such as left ventricular hypertrophy. Catecholamines,

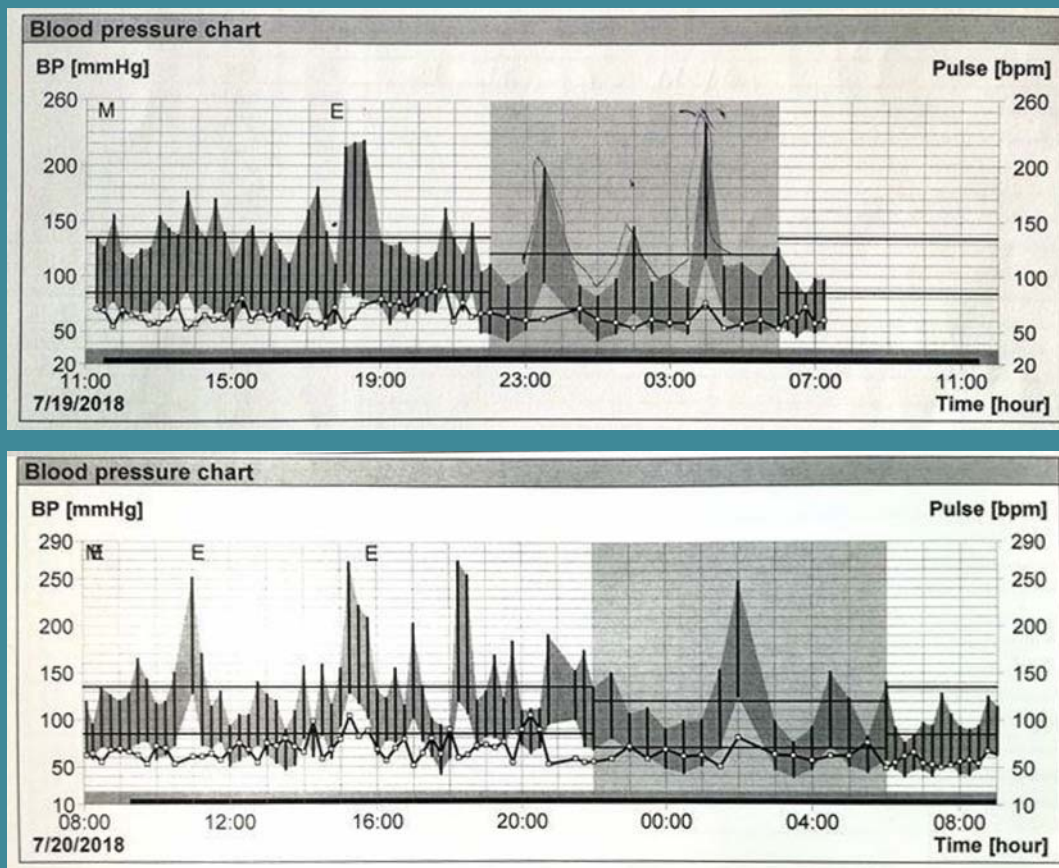


Figure 3. ABPM - Paroxysmal hypertension, followed by hypotension



Figure 4. ECG Holter monitor - multiple premature ventricular contractions



INTERNAL MEDICINE

Clinical Cases

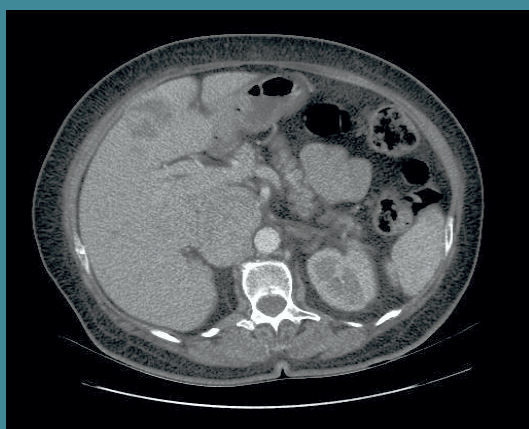


Figure 5.
Abdominal + pelvic CT scan - large tumor in the right adrenal gland



especially norepinephrine, can cause myocardial damage by increasing the oxygen consumption and apoptosis of cardiomyocytes and can further lead to left ventricular systolic dysfunction and dilated cardiomyopathy⁽¹⁵⁻¹⁶⁾. In our case, the patient had already developed target organ damage (left ventricular

hypertrophy with diastolic dysfunction), as seen on the ECG and confirmed by the transthoracic echocardiography and also presented short episodes of ventricular arrhythmias. Therefore, without surgical resection of the tumor, our patient would have been exposed at high risk for major adverse

cardiovascular events and hence the need for prompt surgical intervention, followed by optimal blood pressure control and periodic cardiology follow-up.

Typically, pheochromocytomas are amenable to resection, but carry a recurrence rate of approximately 6,5%-16,5% and surgical resection does not always result in cure, even in benign tumors. A retrospective, single institution study of 135 patients undergoing adrenalectomy for pheochromocytoma and followed for a 14-year period showed that large tumor size (>5 cm) was an independent risk factor for recurrence⁽¹⁷⁾. Unfortunately, we didn't have access to any previous medical records regarding the dimensions of the first tumor. Another study showed that patients who were younger at the time of the first intervention and had right-sided tumors had a higher risk of recurrence, as was the case of our patient⁽¹⁸⁾. Timing of recurrence is also extremely variable, with some recurrences of metastatic disease having been discovered as long as 53 years after the initial surgery⁽¹⁹⁾. Therefore, lifelong surveillance, with annual biochemical tests and/or imaging modalities is needed even after surgical resection⁽²⁰⁾.

Limitations

Following hospital discharge, we had limited access to data regarding the final diagnosis of the liver nodule and the left adrenal gland tumor (benign vs malignant).

Conclusions

Pheochromocytomas should be considered as a possible diagnosis when facing a patient with hypertension (or unexplained hypotension), especially when associated with headaches, excessive sweating and palpitations. If left undiagnosed and without proper treatment,

patients with pheochromocytomas can be at peril due to potentially fatal cardiovascular complications. Surgical resection of the tumor together with the use of alpha- adrenergic and beta-adrenergic blocking agents provide the best line of treatment, but recurrence is still possible. Close follow-up is recommended, with annual blood and urine concentrations of catecholamines.

References

1. Fishbein L, Nathanson KL. Pheochromocytoma and Paraganglioma: Understanding the Complexities of the Genetic Background. *Cancer Genet* 2012;205:1-11.
2. Luca F, Holl N, Vinzio S et al. Manifestations cardiaques des phéochromocytomes. *Ann Endocrinol* 2009;70:43-47.
3. Galetta F, Franzoni F, Bernini G et al. Cardiovascular complications in patients with pheochromocytoma: A mini-review. *Biomed Pharmacother* 2010;64:505-509.
4. Lenders JW, Kerstens MN, Laurence AMAR et al. Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma: A position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens* 2020;38:1443-1456.
5. Prejbisz A, Lenders JW, Eisenhofer G et al. Mortality Associated with Phaeochromocytoma. *Horm Metab Res* 2013, 45;2:154-158.
6. Berends AMA, Eisenhofer G, Fishbein L et al. Intricacies of the molecular machinery of catecholamine biosynthesis and secretion by chromaffin cells of the normal adrenal medulla and in pheochromocytoma and paraganglioma. *Cancers* 2019;11(8):1121.
7. Farrugia FA, Charalampopoulos A. Pheochromocytoma. *Endocr Regul* 2019;53:191-212.
8. Mañas-Martínez AB, Medrano-Navarro AL, Aguillo-Gutiérrez E. Hemorrhagic pheochromocytoma presenting as severe hypertension with myocardial infarction. *Ann Endocrinol* 2017;78:54-6.
9. Manger WM. The protean manifestations of pheochromocytoma. *Horm Metab Res* 2009; 41:658-63.
10. Reisch N, Peczkowska M, Januszewicz A et al. Pheochromocytoma: presentation, diagnosis and treatment. *J Hypertens* 2006;24:2331-9.
11. Galetta F, Franzoni F, Bernini G et al. Cardiovascular complications in patients with pheochromocytoma: a mini-review. *Biomed Pharmacother* 2010;64:505-9.
12. Fleg JL, Evans GW, Margolis KL et al. Orthostatic



INTERNAL MEDICINE

Clinical Cases

Hypotension in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Blood Pressure Trial. Hypertension 2016;68:888-895.

13. Gu YW, Poste J, Kunal M et al. Cardiovascular manifestations of pheochromocytoma. *Cardiol Rev* 2017;25:215-22.

14. Nazari MA, Rosenblum JS, Haigney MC et al. Pathophysiology and acute management of tachyarrhythmias in pheochromocytoma: JACC review topic of the week. *J Am Coll Cardiol* 2020;76:451-64.

15. Gupta MK, Neelakantan TV, Sanghamitra M et al. An assessment of the role of reactive oxygen species and redox signaling in norepinephrine-induced apoptosis and hypertrophy of H9c2 cardiac myoblasts. *Antioxid Redox Signal* 2006;8:1081-93.

16. Y-Hassan S, Falhammar H. Cardiovascular manifestations and complications of pheochromocytoma and paragangliomas. *J Clin Med* 2020;9:2435.

17. Press D, Akyuz M, Dural C et al. Predictors of recurrence in pheochromocytoma. *J Am Coll Surg* 2014;156:1523-1528.

18. Amar L, Servais A, Gimenez-Roqueplo AP et al. Year of diagnosis, features at presentation and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *J Clin Endocrinol Metab* 2005;90:2110-2116.

19. Hamidi O, Young WF, Iñiguez-Ariza NM et al. Malignant pheochromocytoma and paraganglioma: 272 patients over 55 years. *J Clin Endocrinol Metab* 2017;102:3296-3305.

20. Lenders JWM, Duh QY, Eisenhofer G et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915-1942.