REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN CLINICAL CASE

Giant retroperitoneal paraganglioma in a young patient: A multidisciplinary challenge

Manuel García-Sáenz[1], *Daniel Uribe-Cortés*[1], *Aldo Ferreira-Hermosillo*[2], *Claudia Ramírez-Rentería*[2], *Guillermo Montoya-Martínez*[3], *Alicia Estrada*[4], *Katia Hop-García*[5], *Perla Hernandez-Salcedo*[6]

[1]Departamento de Endocrinología, Hospital de Especialidades "Dr. Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI; [2]Unidad de Investigación Médica en Endocrinología Experimental, Centro Médico Nacional Siglo XXI; [3]Departamento de Urología, Hospital de Especialidades "Dr. Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI; [4]Departamento Cirugía General, Hospital de Especialidades "Dr. Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI; [5]Departamento de Patología, Hospital de Especialidades "Dr. Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI; [6]Hospital General Regional No.1. Instituto Mexicano del Seguro Social, México

RESUMEN

Introducción. Una evaluación multidisciplinaria de los paragangliomas es necesaria debido a las potenciales complicaciones relacionadas al tratamiento quirúrgico. Reporte de caso: Un hombre de 26 años de edad se presentó con ansiedad, ataques de pánico, palidez, sudoración y temblor distal con presión arterial de 230/130 mmHg. Las metanefrinas plasmáticas libres se encontraban en 6,392 pg/ml (normal < 149 pg/ml). La tomografía mostró una masa retroperitoneal extra-adrenal de 63 x 51 mm. El manejo preoperatorio fue complicado y durante la cirugía (laparotomía convencional) presentó episodios de hipo e hipertensión. Durante el seguimiento presentó nuevamente hipertensión asociada a estenosis de arteria renal y exclusión renal, sin remanente tumoral. **Conclusión.** Los pacientes jóvenes con paragangliomas tienen una larga expectativa de vida, por lo que se benefician de un diagnóstico temprano, tratamiento integral y vigilancia a largo plazo.

Palabras Clave: Paraganglioma. Gigante. Joven. Retroperitoneal.

ABSTRACT

Introduction: A multidisciplinary evaluation in paragangliomas (PGLs) is required given the potential complications present at the time of diagnosis or related to the surgical management. Case Report: A 26-year-old male, presented with anxiety, panic attacks, pallor, sweating, and distal tremor, BP 230/130 mmHg, was selected. Plasmatic-free metanephrines were 6,392 pg/mL (normal <149 pg/mL), and computed tomography showed an extra-adrenal retroperitoneal mass of 63 × 51 mm. Preoperatory management was difficult and presented hyper- and hypo-tension during surgery (conventional laparotomy). He presented a new episode of hypertension after surgery, that was associated with renal exclusion and without residual tumor. **Conclusion:** Young patients, with PGLs, have long-life expectancies and can benefit from an opportune diagnosis, interdisciplinary management, and prolonged follow-up. (REV MEX ENDOCRINOL METAB NUTR. 2018;5:39-45)

Corresponding author: Manuel Ramón García-Sáenz, manuel.gsm@hotmail.com

Key words: Extra-adrenal paraganglioma. Retroperitoneal neoplasm. Metanephrines.

Dirección para correspondencia:
*Manuel Ramón García-Sáenz
Departamento de Endocrinología
Hospital de Especialidades "Dr. Bernardo Sepúlveda"
Centro Médico Nacional Siglo XXI
E-mail: manuel.gsm@hotmail.com

Fecha de recepción: 15-01-2018
Fecha de aceptación: 08-02-2018

INTRODUCTION

Neuroendocrine tumors arising from the adrenal medulla and extra-adrenal ganglia are called pheochromocytomas and paragangliomas (PCCs/PGLs)[1]. They occur in 0.2-0.6% of hypertensive patients and account for up to 5% of adrenal incidentalomas[2]. PGLs originate from paraganglia at a number of anatomical sites, including the head, neck, thorax, and abdomen, and depending on their anatomic distribution, they could be divided into three groups: branchiomeric, intravagal, and aorticosympathetic[3].

PGLs may occur at any age, with the highest incidence between 40 and 50 years and with an approximately equal sex distribution[4]. At least one-third are hereditary, and this percentage is likely to increase with the discovery of new susceptibility genes[5]. In fact, patients younger than 35 years of age at the time of diagnosis are more likely to have a genetic abnormality[6]. Other characteristics associated to germline mutations are a family history of paraganglial tumors and the presence of multiple tumors[7].

Aorticosympathetic PGLs or extra-adrenal PCCs are located along the side of the aorta and are associated with the sympathetic nervous system. They secrete and store catecholamines. Symptoms such as hypertension, flushing, sweating, headache, diaphoresis, anxiety, tachycardia, or palpitations are symptoms reported in patients with increased catecholamine secretion in functional tumors[8]. However, PGLS are called "the great masquerader"[9] due to their variable clinical presentation. The symptoms vary depending on the predominant catecholamine produced by the tumor or desensitization of adrenoreceptors[7].

The treatment of choice for functional PGLs is laparoscopic resection, but in case of a large tumor (> 6 cm) with a high risk of malignancy, conventional laparotomy or even "in-block" resection must be considered, after an adequate presurgical treatment with α-blockade and β-blockade to reduce perioperative mortality to < 1%[10]. A multidisciplinary evaluation is required, given the potential cardiovascular complications that may already be present at the time of diagnosis or related to the medical and surgical management. Cardiovascular, renal, or psychiatric comorbidities associated with catecholamine excess may complicate the treatment and should be considered at all times. Anesthetic management may be difficult since the tumor may shift from hypertensive crisis to hypotensive shock within minutes. Usually, blood pressure (BP) normalizes after the operation, depending on the completeness of the resection, duration of pre-existing hypertension, and potentially coexisting causes[11].

We present a clinical case of a young patient, with a diagnosis of secondary hypertension by a giant catecholamine-producing paraganglioma that grew adjacent to important vascular structures. The initial medical management followed by the surgical and postsurgical management can be very difficult and represent a multidisciplinary challenge.

CASE REPORT

A 26-year-old male, presented with a 5-year history of headache and palpitations episodes. He has an aunt with a history of medullary thyroid carcinoma and a twin brother who was reported to be healthy. Five months before first examination, he reported severe anxiety, panic attacks, pallor, sweating, and distal tremor and was treated with fluoxetine with poor response. A cardiologist evaluated him for tachycardia (heart rate [HR] of 110 beats per minute [bpm]) and hypertension (BP of 140/90 mmHg). He prescribed propranolol, which increased the symptoms (BP 230/130 mmHg and HR 140 per minute). Considering the age of the patient, the presence of paroxysms, and exacerbation with β-blockade, he considered the possibility of endocrine hypertension and referred him to an endocrinologist.

At his arrival to the Endocrinology Department, the laboratory tests evidenced markedly elevated plasma metanephrines (Table 1). The abdominal computed tomography (CT) demonstrated a retroperitoneal tumor of 63 × 51 mm that displaced adjacent structures, compressed the cava vein, and surrounded 40% of the aorta (Fig. 1).

Table 1. Biochemical evaluation of the patient at the beginning, as well as follow-up at 3 months.

	Initial	3 months of follow-up	Reference
Glucose	93 mg/dL	89 mg/dL	60-100 mg/dL
Creatinine	0.97 mg/dL	1.48 mg/dL	0.4-1.2 mg/dL
Plasmatic free-metanephrine	6,932 pg/mL	88.52 pg/mL	<149 pg/mL
Plasmatic norepinephrine	14,547 pg/mL		<600 pg/mL
Plasmatic epinephrine	563 pg/mL		<125 pg/mL
Plasmatic dopamine	86 pg/mL		<100 pg/mL
Urinary metanephrine		23 mcg/24 h	25-312 mcg/24 h
Urinary norepinephrine	3,539 mcg/24 h		<90 mcg/24 h
Urinary epinephrine	37 mcg/24 h		<20 mcg/24 h
Urinary dopamine	119 mcg/24 h		<600 mcg/24 h
Calcitonin	4.1 pg/mL	4.37 pg/mL	<8.4 pg/mL
Carcinoembryonic antigen	0.9 ng/mL	1.1 ng/mL	0.2-10.0 ng/mL
Free-thyroxine	1.34 ng/dL	1.16 ng/dL	0.93-1.7 ng/dL
Thyroid-stimulating hormone	1.61 mcUI/mL	1.53 mcUI/mL	0.27-4.2 mcUI/mL

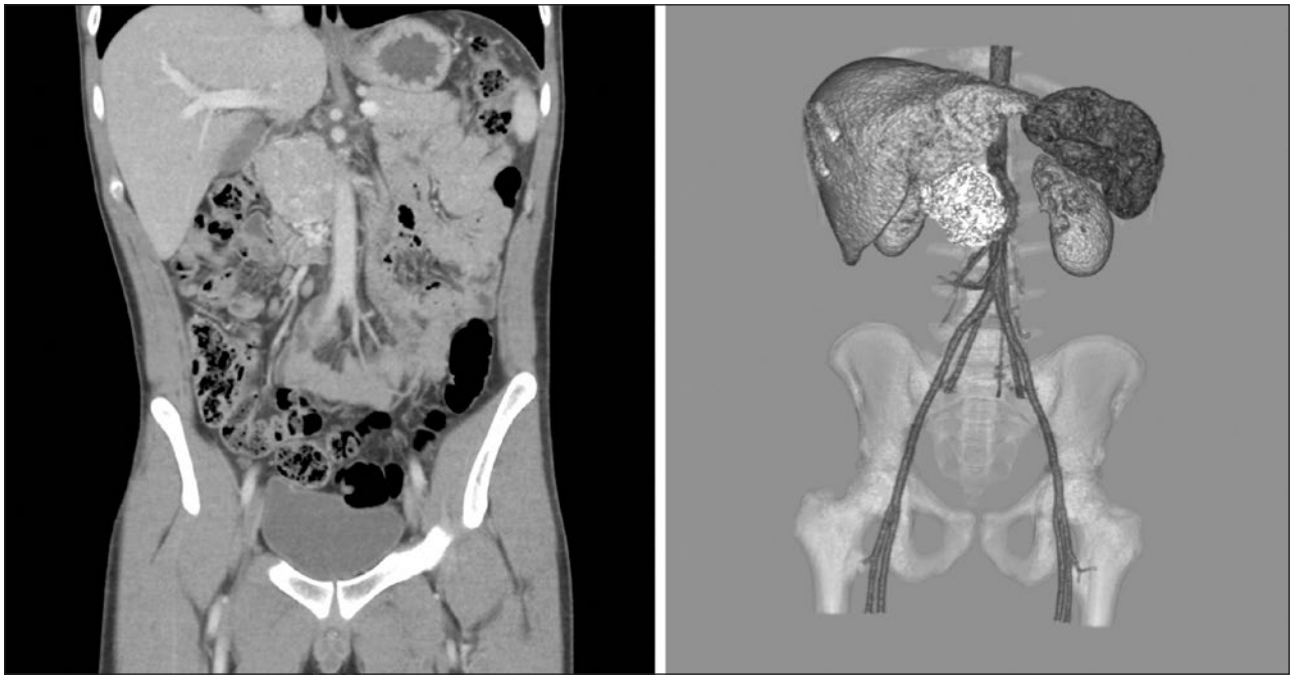

Figure 1. Computed tomography (CT) in coronal section **(A),** where 63 × 51 mm ovoid imaged is evidenced, with reinforcement when administering contrast material, in close relationship with vascular structures and causing displacement. The second image **(B)** shows a three dimensional reconstruction where the relation with vascular structures is better evidenced.

We prescribed a sequential management with increasing doses of prazosin (the only a-blockade available, since phenoxybenzamine and doxazosin are not currently for sale in Mexico) and then nifedipine (calcium channel blocker). However, the patient had a low tolerance to prazosin and frequent adrenergic spells associated with panic attacks (more than 4 per day); hence, we decided to hospitalize him for supervised and intensive management. Between spells he had a BP of 90/60 mmHg in supine position and 80/50 mmHg in bipedestation, and he also presented tachycardia during the first few minutes after standing up. The patient was treated with intravenous fluid therapy (1 L of saline

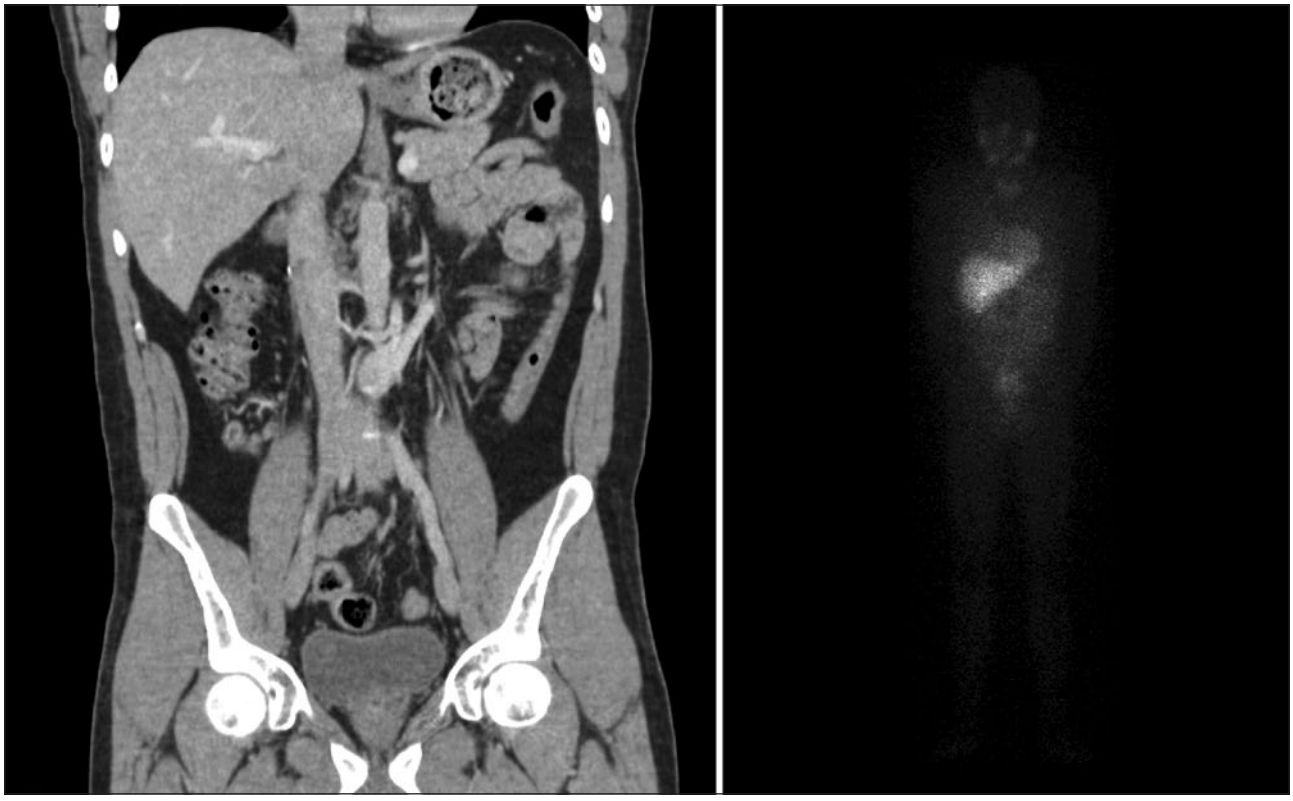

Figure 2. Post-surgical computed tomography without evidence of residual mass **(A)**, and MIBG scintygraphy with no abnormal uptake **(B)**.

solution 0.9% every 4 h) for 4 days until postural changes in BP normalized. After the prazosin and nifedipine therapies were optimized (12 and 60 mg/day, respectively), the patient continued with tachycardia, so we added propranolol and increased it to a final dose of 160 mg/day.

The retroperitoneal tumor was surgically removed by laparotomy. During surgery, tachycardia and hypertensive crisis presented up to 192 bpm and 310/170 mmHg, requiring the use of intravenous antihypertensive (esmolol and sodium nitroprusside), without cardiac involvement, subsequently presenting hypotension in need for vasopressor drugs in continuous infusion. During the immediate post-surgical evaluation, he maintained normal BP with intravenous solutions and without anti-hypertensive treatment. However, 96-h after surgery, he presented again with hypertension (BP of 140/90 mmHg), without adrenergic symptoms or evidence of a residual tumor in the CT (Fig. 2). Nevertheless, the right kidney was found to have small dimensions, and functional renal exclusion was documented by scintigraphy. The final evaluation concluded that the renal artery had been accidentally ligated during the surgical procedure and prescription with losartan 100 mg/day improved the BP significantly.

The histopathology reported paraganglioma of 6.5 $\times$ 4.5 $\times$ 4.2 cm and weight of 41 gr, with capsular invasion, without vascular invasion, necrosis or mitosis (Fig. 3).

Three months after surgery, he had normal plasmatic and urinary metanephrines levels (88.52 pg/mL and 23 mcg/24 h, respectively). During the last evaluation, a year after the initial symptoms, the patient's brother presented mild hypertension and increased serum metanephrines (twice the upper limit of normal). There is no evidence of abdominal paraganglioma, but he continues to be under evaluation. Neither brother presents thyroid nor parathyroid abnormalities and other endocrinopathies and neoplasias have not been found after 18 months of follow-up.

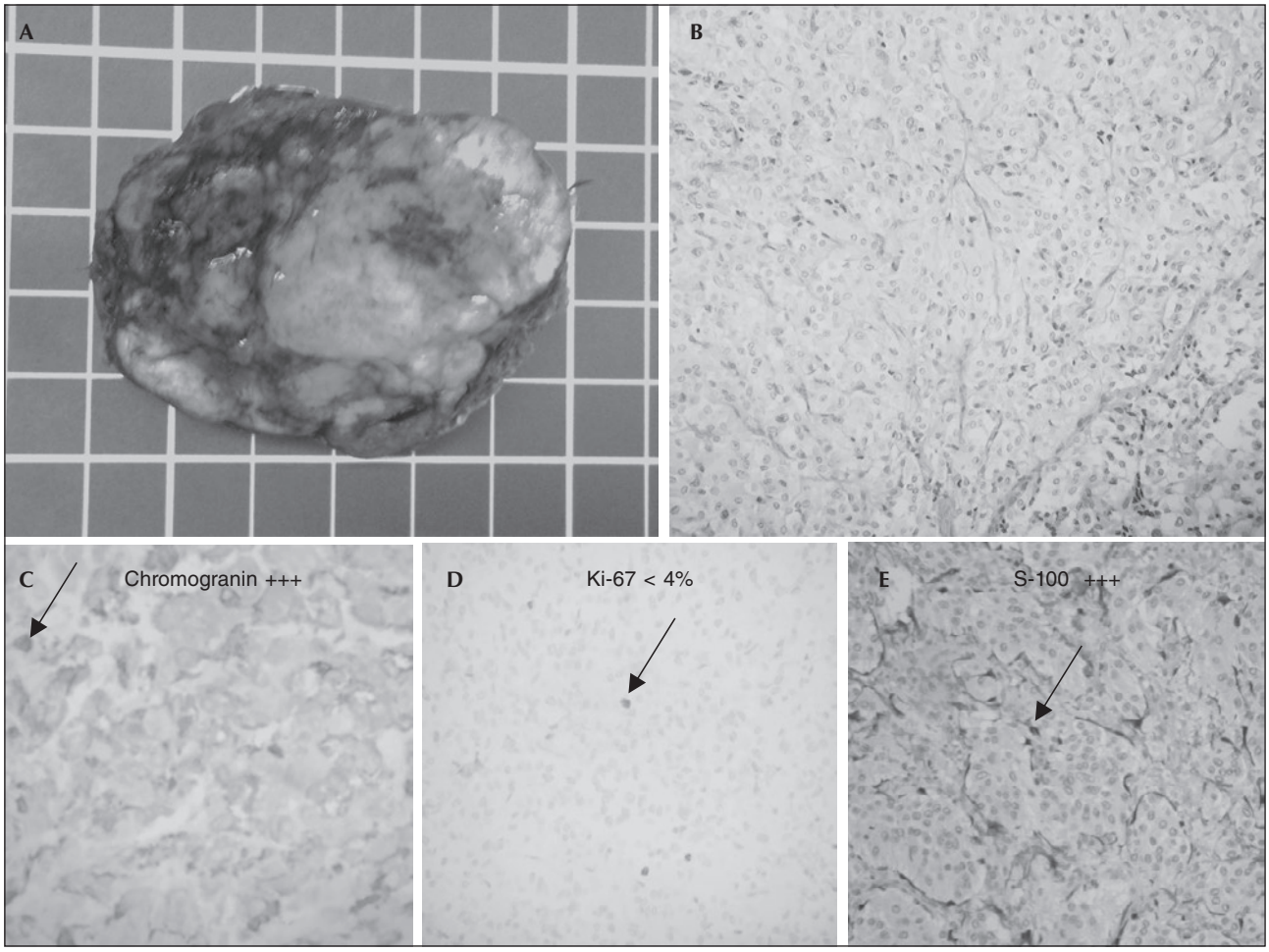

Figure 3. Macroscopic view of paraganglioma **(A)**, a histopathology view with epithelioid cells, surrounded with stromal septa **(B)** positive chromogranin A (C), Ki67 < 4% **(D)** and positive s-100 **(E)**. Arrows show positivity in immunohistochemistry

DISCUSSION

The majority of thoracoabdominal PCCs/PGLs produce catecholamines; however, advanced cases cause symptoms related to the catecholamine excess. Some of them may remain undiagnosed for years because of the small amount of hormones produced by the tumor, which are in turn degraded to metanephrines and not liberated to the general circulation. Furthermore, some tumors produce paroxistical release of catecholamines which generates intermittent symptoms and variable laboratory results. The clinical presentation may also vary because of the different profiles of catecholamines secreted, the mass effect generated by the tumor on others organs, if they present as part of a genetic syndrome or they may even be asymptomatic if desensitization of adrenoreceptors is present (due to long-term exposure to high circulating catecholamine). Typical symptoms are paroxysms of severe headache, palpitations, and diaphoresis, commonly called "the classic triad" which has a high specificity for the diagnosis of pheochromocytoma and paraganglioma but is not present in all cases. The symptoms may be insidious or atypical, leading to a long delay in diagnosis[12]. In fact, our patient has a delay in diagnosis of nearly 6 years, considering that the psychiatric symptoms were initially associated to anxiety and stressful conditions, "luckily" the use of β-blockers resulted in unopposed alpha vasoconstriction, which leads to worsening hypertension and a clinical suspicion of endocrine hypertension. Adverse

events related to beta blockers are frequent in these tumors, and the diagnosis of catecholamine excess should be considered in any patient presenting them, even if they are otherwise asymptomatic.

The laboratory tests were consistent with that described in the literature, with a predominance of norepinephrine/epinephrine and their metabolite (metanephrines). PGLs exhibit different biochemical properties: meanwhile, PCCs mainly produce epinephrine and norepinephrine, and the malignant PGLs can produce norepinephrine, dopamine, or no catecholamines due to a de-differentiation of the enzymatic machinery[13].

The hereditary component is important; however, our patient does not have any family member with confirmed diagnosis of malignant tumors and he did not have any other lesions or metastasis. Although it is currently considered that up to 24% of sporadic PCCs/PGLs have germline mutations, there is no consensus to determine who should undergo the test and for what genes. In this particular case, we consider that the patient is a candidate for genetic testing because of his young age and also because of the history of his twin brother having mildly elevated catecholamines and another family member with medullary thyroid carcinoma. Some authors considered that young patients (below 45 years of age) with extra-adrenal tumor location, and multiple tumors have five- to eight-fold increased likelihood of mutation. An algorithm and a genetic sequencing panel proposed to include 10 gene mutations: *MAX, MEN1, NF1, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127*, and *VHL*[14]. We would consider testing for *VHL, SDHB, SDHC,* and *SDHD* in our patient, because the extra-adrenal presentation with norepinephrine phenotype increases the chances of having these tumors mutated; however, we do not have the possibility of carrying out this study in our center.

The first indication of α-blockade for PCCs/PGLs was described in 1956, and it is currently recommended for all patients with functional PCCs/PGLs of catecholamine release during surgical extirpation and β-blockade, calcium channel blockade, or angiotensin receptor blockade could be considered as second options. In our patient, the purpose of treatment was to maintain a systolic BP (SBP) < 130 mmHg seated but > 90 mmHg while standing, and HR between 60 and 70 bpm sitting and 70-80 bpm while standing, according to international guidelines[11]. Discussion remains on to whether the alpha and beta blockades change the overall risks and results of the surgery; however, uncontrolled severe hypertension, especially severe and continuous crisis such as that presented by the patient, is an indication to start treatment to optimize BP control just like in any other hypertensive patient heading for elective surgery, with the particularity that BP must be treated in a specific sequential order of drugs[15]. The treatment may be omitted in patients with non-functional head and neck PGLs or it may be considered effective with alpha blockers if the patient does not present with tachycardia[3].

Intraoperatively, hypertensive episodes are related with catecholamine release, mostly by direct manipulation of the tumor, defining "hypertensive episode" as SBP that increased 30% above the baseline or SBP of 200 mmHg or higher, and "hypotensive episode" was defined as SBP that decreased below 80 mmHg[10]. Both episodes were observed in our patient which is a dangerous occurrence that was resolved by an adequate intraoperative management by anesthesiology. The necessary drugs to treat these BP variations are not part of the "everyday drugs" used by all anesthesiologists in our institution; therefore, we recommend that the anesthesiologist and the intensive care unit should be informed days before surgery to have an adequate supply of drugs available at the time of the surgery.

Post-operative morbidity is higher in PGLs than PCCs, and these differences may be partly due to a number of challenges in removing PGLs, including the diversity in their location, greater difficulty in operative exposure, and proximity to other major structures, including the aorta, vena cava, renal vessels, and ureters[16]. Factors observed in our patient, such as the invasion of neighboring structures, adherence to vascular structures, and the difficulty in manipulating adjacent tissues, culminated in the involvement of vascular structures of related organs with the final presence of renal exclusion and renovascular hypertension. The differential diagnosis of the recurrent hypertension in this case was performed with the help of anatomic and functional

tests. The apparent resolution for a few days and the absence of clinical data related to excessive catecholamine production lead to the suspicion that the BP elevation was not related to a tumoral source.

The Clavien-Dindo's classification has been used to assess the severity of post-operative complications, since, as previously mentioned, the conditions of the extra-adrenal lesions mainly favor vascular lesions, previously describing quilorrhea and renal vessel lesions[17], which most probably was the cause of renal failure in our patient, generating a different cause of secondary hypertension with a different treatment and prognosis.

Despite the fact that our patient presented complications associated with the surgical procedure resulting from the difficulties in the resection of the tumor, his condition has improved significantly, since the hypertension is not difficult to control, and has a lower cardiovascular risk due to lack of hypertensive crises. Preservation of the function of the remaining kidney is of particular importance in the context of chronic hypertension. This issue, as well as the fact that the patient also presented with factors associated with an increased risk of malignancy, determines the need for a prolonged follow-up. Endocrinologists should remember that recurrences are not always heralded by hormone-related symptoms or biochemical evidence of paraganglioma. Some tumors require a critical mass to be symptomatic or detected by current laboratory tests; therefore, evaluation should also include routine imaging tests which may be done even in 3-year intervals if the patient is asymptomatic[18,19].

Finally, considering an evaluation of the patient and his brother is important for the prognosis, since syndromic affections may not appear synchronically or they could present other form of tumor (not necessary to catecholamine-producing mass).

CONCLUSION

It is essential to remember the indications to study endocrine causes of secondary hypertension. Even when PGLs are rare causes, young patients, with a long life expectancy, can benefit from an opportune diagnosis when they have small tumors with little invasion or dissemination (either benign or malignant). Genetic testing is ideal in many cases, but careful clinical evaluation and follow-up of suspicious cases may also yield good results when the resources are unavailable.

REFERENCES

1. DeLellis RA, Lloyd RV, Heitz PU, et al. World Health Organization Classification of Tumors. Pathology and Genetics of Tumours of Endocrine Organs. Lyon, France: IARC Press; 2004. p. 99-102.
2. Kasperlik-Zaluska AA, Roslonowska E, Slowinska-Srzednicka J, et al. 1,111 patients with adrenal incidentalomas observed at a single endocrinological center: incidence of chromaffin tumors. Ann N Y Acad Sci. 2006;1073:38-46.
3. Jabangir N, Shirazi B. Paraganglioma: a diagnostic dilemma. J Pak Med Assoc. 2010;60:789-91.
4. Mannelli M, Castellano M, Schiavi F, et al. Clinically guided genetic screening in a large cohort of Italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. J Clin Endocrinol Metab. 2009;94:1541-7.
5. Gimenez-Roqueplo AP, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. Horm Metab Res. 2012;44:328-222.
6. Burnichon N, Rohmer V, Amar L, et al. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. J Clin Endocrinol Metab. 2009;94:2817-27.
7. Neumann HP, Eng C. The approach to the patient with paraganglioma. J Clin Endocrinol Metab. 2009;94:2677-83.
8. Rakonjac N, Marković S. Paraganglioma – a cause of hypertension in a young patient. Vojnosanit Pregl. 2012;69:721-4.
9. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev. 1994;15:356-68.
10. Niemann U, Hiller W, Behrend M. 25 years experience of the surgical treatment of phaeochromocytoma. Eur J Surg. 2002;168:716-9.
11. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;170:109-19.
12. Corssmit EP, Romijn JA. Clinical management of paragangliomas. Eur J Endocrinol. 2014;171:R231-43.
13. Brouwers FM, Eisenhofer G, Tao JJ, et al. High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. J Clin Endocrinol Metab. 2006;91:4505-9.
14. Fishbein L, Merril S, Fraker DL, et al. Inherited mutations in pheochromocytoma and paraganglioma: shy all patients should be offered genetic testing. Ann Surg Oncol. 2013;20:1444-50.
15. Garg MK, Kharb S, Brar KS, Gundgurthi A, Mittal R. Medical management of pheochromocytoma: role of the endocrinologist. Indian J Endocrinol Metab. 2011;15:329-36.
16. Hattori S, Miyajima A, Hirasawa Y, et al. Surgical outcome of laparoscopic surgery, including laparoendoscopic single-site surgery, for retroperitoneal paraganglioma compared with adrenal pheochromocytoma. J Endourol. 2014;28:686-92.
17. Wang J, Li Y, Xiao N, et al. Retroperitoneoscopic resection of primary paraganglioma: single-center clinical experience and literature review. J Endourol. 2014;28:1345-51.
18. Castinetti F, Kroiss A, Kumar R, Pacak K, Taieb D. Imaging and imaging-based treatment of pheochromocytoma and paraganglioma. Endocr Relat Cancer. 2015;22:135-45.
19. Wen J, Li HZ, Ji ZG, et al. A decade of clinical experience with extra-adrenal paragangliomas of retroperitoneum: report of 67 cases and a literature review. Urol Ann 2010;2:12-6.