# Paraganglioma Retroperitoneal: Um Caso de Hipertensão Secundária

## *Retroperitoneal Paraganglioma: A Case of Secondary Hypertension*

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## Resumo:

O paraganglioma é um tumor raro e de crescimento insidioso, que advém de gânglios parassimpáticos e simpáticos extraadrenais. Os paragangliomas simpáticos usualmente secretam catecolaminas e habitualmente estão localizados no abdómen, enquanto os paragangliomas parassimpáticos são na sua maioria não-secretores e localizam-se habitualmente no pescoço e na base do crânio. Apresentamos o caso de um homem de 36 anos seguido em consulta externa por hipertensão arterial que tinha níveis elevados plasmáticos e urinários de noradrenalina e seus metabolitos. Tomografia computorizada revelou uma massa retroperitoneal hipervascularizada adjacente à porção inferior da artéria renal direita, com textura heterogénea, e calibre de artéria renal e tamanho de rins assimétricos (direito mais pequeno que esquerdo). O nosso objectivo é o de realçar a importância de um estudo aprofundado de causas secundárias e como a detecção precoce e tratamento destes tumores, em adição com estudos genéticos familiares, podem ajudar a prevenir morbilidade e mortalidade.

**Palavras-chave:** Hipertensão/etiologia; Neoplasias Retroperitoneais/complicações; Paraganglioma/complicações.

## *Abstract:*

*A paraganglioma is a rare, slow-growing neoplasm that originates in extra-adrenal parasympathetic or sympathetic ganglia. Sympathetic paragangliomas usually secrete catecholamines and are generally located in the abdomen, while parasympathetic paragangliomas are mostly non-secreting and usually located in the neck and the base of the skull. We describe the case of a 36-year-old man in outpatient follow-up for arterial hypertension who presented with elevated levels of plasmatic and urinary noradrenaline and its metabolites. Computerized tomography scan revealed a hypervascular retroperitoneal mass adjacent to the inferior portion of the right renal artery, with heterogeneous texture, and asymmetrical renal artery caliber and kidney size (right smaller than left). Our aim is to highlight the importance of a thorough work-up on secondary causes of hypertension and how early detection and treatment of these neoplasms, paired with familial genetic studies, can help prevent morbidity and mortality.*

***Keywords:*** *Hypertension/etiology; Paraganglioma/complications; Retroperitoneal Neoplasms/complications.*

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## Introduction

A paraganglioma is a rare, slow-growing neoplasm that originates in extra-adrenal parasympathetic or sympathetic ganglia. Sympathetic paragangliomas usually secrete catecholamines and are generally located in the abdomen, while parasympathetic paragangliomas are mostly non-secreting and usually located in the neck and the base of the skull.[1,2] According to the 2017 World Health Organization (WHO) classification, paragangliomas are histologically indistinguishable from pheochromocytomas and can only be differentiated by anatomical location, seeing as the latter are adrenal tumors.[1]

Clinical presentation varies according to location and degree of catecholamine secretion. They are usually a single sporadic unilateral neoplasm but a considerable percentage of 30% to 40% can be familial and associated with genetic syndromes such as familial paraganglioma syndrome, von-Hippel Lindau or MEN2.[2,3] Diagnosis is based in proof of excessive production of catecholamine and its metabolites and followed by imaging with computed tomography (CT) and/or magnetic resonance. Surgical removal is the cornerstone of treatment. Lifelong outpatient follow-up is indicated due to possibility of recurrence after surgical removal.[2,3]

## Case Report

A 36-year-old otherwise healthy male patient was referenced to a specialized arterial hypertension consultation. He had a history of 2 years of hypertension and was currently medicated with indapamide, a thiazide-like diuretic, without optimal blood pressure control. He had no symptoms namely headaches, tachycardia, chest pain or hyperhidrosis. Physical examination was unremarkable, with no palpable masses, heart or abdominal murmurs, and blood pressure values in both arms were equivalent.

Amlodipine was associated and diagnostic work-up was requested. Laboratory studies revealed a markedly elevated and urinary noradrenaline secretion of 2774 pg/mL (normal value of 300-650 in orthostatism) and 897 µg /24 hours

(normal value under 76), respectively. Plasmatic and urinary normetanephrine, a noradrenaline metabolite, was also high with values of 2287 pg/mL (normal value under 196) and 3534 µg /24 hours (normal value under 444), respectively. Aldosterone (72.15 ng/dL; reference range of 6.80–17.3 ng/dL), plasmatic renin (455.8 mUI/L; reference range of 2.8–39.9 mUI/L) and plasmatic renin activity (37.98 ng/mL/h; reference range of 0.50–1.70 ng/mL/h) were also markedly elevated, whereas cortisol (25.75 ug/dL; reference range of 4.3–22.4 ug/dL) and ACTH (57.40 pg/mL; normal value under 46) values were just slightly elevated and thyroid hormone levels and urea/creatinine were within the normal range. A contrast enhanced abdominal and pelvic CT scan was requested which disclosed the presence of a retroperitoneal hypervascular and heterogeneous mass adjacent to the inferior portion of the right renal artery measuring 39 by 17 mm (Fig. 1). Both kidneys were asymmetrical, with the right one being of smaller size (bipolar diameter of 78 mm *versus* the left kidney's diameter of 137 mm) and both renal arteries also had asymmetrical caliber, with a difference of 3 mm favoring the left artery. Renal function was normal with a creatinine level of 1.1 mg/dL. No adrenal hyperplasia or adenoma was found or signs of fibromuscular dysplasia of the renal arteries. A diagnosis of paraganglioma was made. Genetic study revealed a pathogenic variant in the gene encoding succinate dehydrogenase complex subunits B (*SDHB*). $^{18}$F-FDG PET/CT scan confirmed hypermetabolic activity corresponding to the retroperitoneal mass, with no secondary lesions. Collaboration with endocrinology and general surgery was requested as multidisciplinary care would be key in managing perioperative alpha and beta blockade.

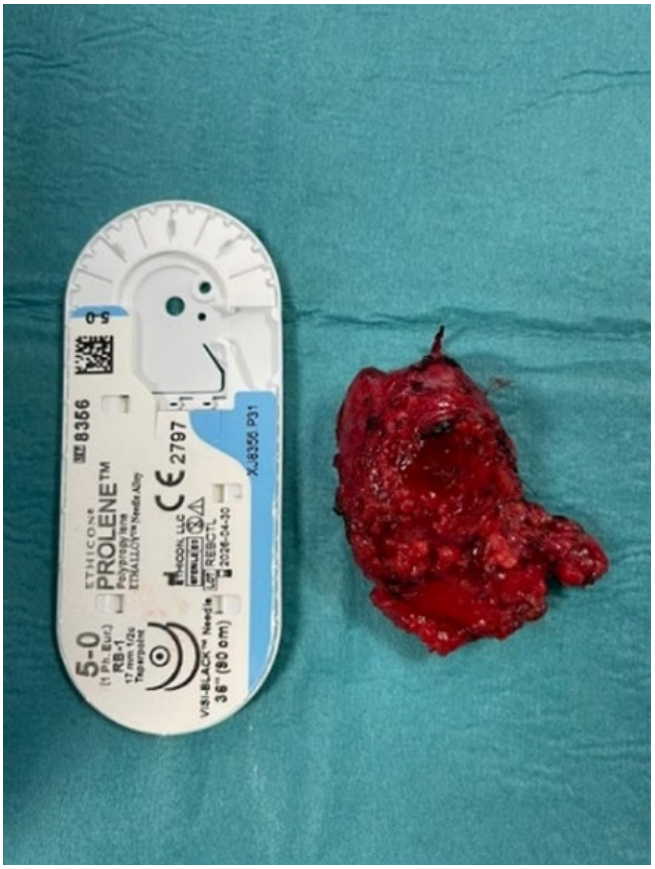


**Figure 1**: Paraganglioma after laparatomic excision with 5-0 sutures for size reference.

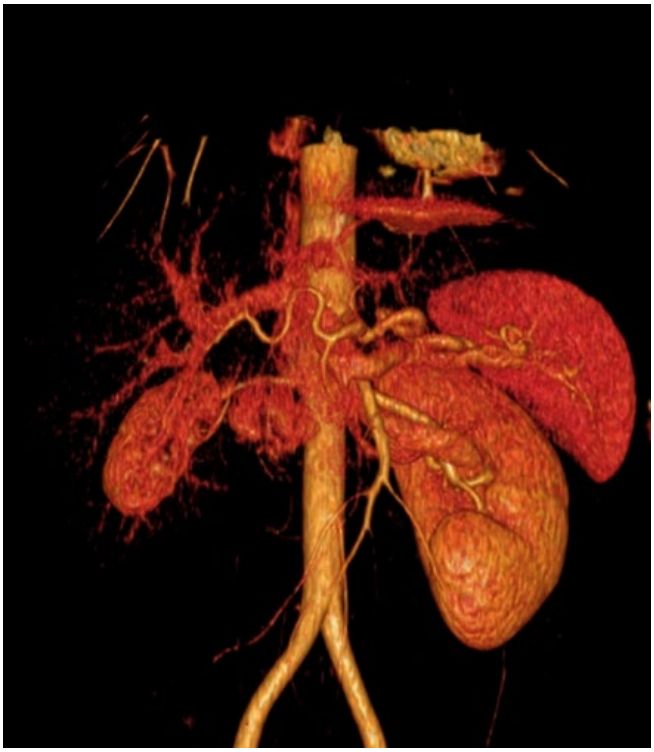

**Figure 2**: Retroperitoneal hypervascular mass (*) below the right renal artery.

Phenoxybenzamine was started 2 weeks prior to surgery with dose titration to a maximum of 70 mg a day. Propranolol was added after adequate alpha blockade was obtained due to significant tachycardia and adjusted to a maximum dose of 30 mg. Laparotomic exeresis of the retroperitoneal paraganglioma was successful (Fig. 2).

Histological analysis confirmed the diagnosis of paraganglioma, with no signs of vascular or capsular invasion. In the post operative stage, the patient needed transient aminergic support with noradrenaline due to refractory hypotension. The patient maintained hemodynamic stability while in the infirmary, with no need for anti-hypertensive medication, which was ultimately suspended at hospital discharge. Post-op plasmatic renin, noradrenaline and normetanephrine levels showed a steep decline with renin levels of 30.52 mU/L (previous 455.80 mU/L), noradrenaline levels of 501 pg/ml (previous of 2774 pg/mL) and normetanephrine levels of 281 pg/mL (previous of 2287 pg/mL) (Table 1). Ambulatory blood pressure levels and in outpatient observation were normal. The patient awaits ambulatory blood pressure monitoring exam, abdominal CT scan, renal ultrasound with Doppler and Genetics consultation for counseling.

**Table 1**: Pre-op *versus* post-op renin and catecholamine levels.

| Blood test | Pre-op | Post-op | Reference range |
|---|---|---|---|
| Renin | 455.80 | 30.52 | 2.8 – 39.9 mUI/L |
| Noradrenaline | 2774 | 501 | 300 - 650 pg/mL |
| Normetanephrine | 2287 | 281 | <196 pg/mL |

## Discussion

Paragangliomas are rare neoplasms, histologically indistinguishable from pheochromocytomas but differentiable through their extra-adrenal location.[1,2]

Sympathetic paragangliomas, like the one presented in this case, are usually located in the abdomen, and secrete catecholamines, whose excessive production is the basis of the diagnostic work-up.[1,2] Their estimated incidence is of 1 patient in 300 000, with an average age at diagnosis of 40 years-old and an incidence interval of 30 to 50 years of age, with no gender differences.[3] Seeing as an estimate of 40% to 60% of diagnosed patients have a germline mutation, which associates with an added risk of transmission and malignancy, genetics studies are key.[2] This is very particular in young patients with family history of hypertension, syndromic features or metastatic paragangliomas. Our patient's genetic study revealed a pathogenic variant in the gene encoding succinate dehydrogenase complex subunits B (*SDHB*) which is associated with familial paraganglioma syndromes.[2,3] This *SDHB* mutation presents the greatest risk of malignancy hence the importance of pre-op work-up and detection of secondary lesions.

Our patient had asymmetrical kidneys and renal arteries disfavoring the right side. This fact was in probable relation to the location of the paraganglioma, which by being adjacent to the right renal artery was most likely responsible for its smaller caliber and reduced blood flow. By creating an extra-renal constriction of the right renal artery, renin excretion was thoroughly enhanced, which justifies why, while not being associated with paragangliomas, we encountered an elevated level of renin and plasmatic renin activity, which steeply declined after surgical removal.[4] In regard to the perioperative management of catecholamine secreting neoplasms, it includes alpha- and beta-adrenergic antagonists in order to prevent hypertensive crisis in the intraoperative setting as well as optimized fluid therapy to avoid steep decline in perioperative blood pressure.[5] Preoperative preparation may take up to 15 days.

Phenoxybenzamine is a non-selective alpha-receptor antagonist, usually initiated at doses of 10 mg every 6 to 12 hours and increased to 30-40 mg every 6 hours to a maximum of 240 mg daily.[5] In this case doses were titrated to a daily total of 70 mg, with optimal blood pressure objectives achieved.

These objectives can vary with author preferences and institutional protocols and consist in a systolic blood pressure value below 130 mmHg, diastolic values below 80 mmHg and a heart rate below 80 beats per minute.[5] Tachycardia is a

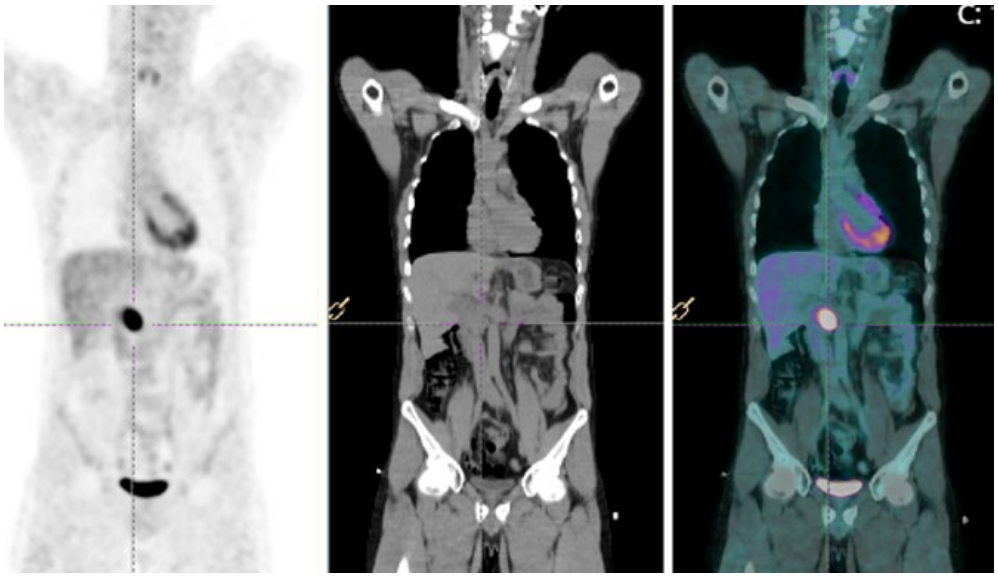

**Figure 3**: $^{18}$F-FDG PET/CT scan revealing hypermetabolic mass below the right renal artery.

common side effect, more frequently encountered with phenoxybenzamine than with selective alpha blockade medication which is why beta-receptor antagonists are needed. They must only be initiated after alpha-blockade is started seeing as suppression of beta-1 mediated cardiac sympathetic drive before adequate arteriolar dilatation can lead to acute cardiac insufficiency and pulmonary edema.[5]

The incidence of postoperative hypotension requiring vasopressor support is also greater in non-selective alpha--receptor antagonists, which was the case. Propranolol is usually titrated to a dose of 40 to 240 mg a day.[5] Alpha and beta blockade was present right up to the day before surgical removal. There are several different imaging acquisition techniques ranging from CT and magnetic resonance imaging (MRI) to $^{18}$F-DOPA, $^{68}$Ga-DOTA or $^{18}$F-FDG PET/CT and $^{123}$I-MIBG scintigraphy.[6] Most authors recommend $^{18}$F-DOPA or $^{68}$Ga-DOTA PET/CT scan followed by 1$^{8}$F-FDG PET/CT as a formal diagnostic imaging method, with availability being dependent on each hospital's resources. $^{18}$F-DOPA PET has higher sensitivity than $^{123}$I-MIBG scintigraphy, and is more specific than $^{18}$F-FDG PET, although the latter is more frequently helpful in metastatic disease with *SDHB* mutations (83% sensitivity per lesion).[6] In this case full-body $^{18}$F-FDG PET/CT scan revealed no metastatic lesions (Fig. 3). Paragangliomas can recur up to 20 years after initial presentation which is why lifetime outpatient follow-up with regular catecholamine and metanephrine work-up and imaging is warranted.[2] CT and MRI suffice in follow-up imaging although PET/CT scan follow-up as an initial choice is rising, particularly in patients with previously positive PET results.[2] ■

### Declaração de Contribuição

JRL – Elaboração do artigo, concepção, desenho, recolha de dados e revisão da literatura
EA – Revisão da literatura e do artigo
MP – Recolha de dados e revisão do artigo
RS, SC – Revisão do artigo
Todos os autores aprovaram a versão final

### Contributorship Statement

JRL – Preparation of the article, conception, design, data collection and literature review.
EA – Literature review and article
MP – Data collection and article review
RS, SC – Article review
All authors approved the final version

### Responsabilidades Éticas

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