

## Pheochromocytoma: A Great Simulator. Small Series of A Single Institution

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### ABSTRACT

**Background:** pheochromocytoma is a catecholamine-secreting neuroendocrine tumor, with usual origin in the adrenal medulla. They are mostly diagnosed as adrenal incidentalomas in abdominal tomography (CT) or magnetic resonance imaging (MRI) or by related symptoms, as the classic triad including headaches, profuse sweating, and palpitations. Although it is a rare cause of secondary hypertension, this occurs in a great proportion of patients and it is usually sustained and paroxysmal. The biochemical diagnosis requires the dosage of plasmatic and/or urinary metanephrines and once confirmed, an imaging study such as CT or MRI must be requested to determine its location. Pheochromocytoma usually has low metastatic potential; treatment is adrenalectomy, conventional or laparoscopic, and resection can be curative. The reason for presenting these cases is to show two forms of presentation of a rare disease, with normal or hypertension, even in large tumors.

**Cases:** We present four cases of Pheochromocytoma, two of which were diagnosed due to secondary hypertension and two as adrenal incidentalomas. In two of them the concomitant diagnosis of panic attacks and anxiety attacks was made, which sometimes shares clinical symptoms with the clinical picture of catecholamine's excess.

A 31-year-old man presents who presented with resistant hypertension and paroxysmal adrenergic crisis.

A 46-year-old woman who presented with hypertension difficult to treat and adrenal incidentaloma.

A 35-year-old woman who had big adrenal incidentaloma and normal blood pressure.

A 34-year-old woman developed panic attacks and was found an adrenal incidentaloma on CT without hypertension.

**Conclusion:** pheochromocytoma is a rare tumor that can have variable clinical presentations, with low malignant potential in the majority of the cases, and its accurate treatment relays on the clinical suspicion of this entity.

**Keywords:** Pheochromocytoma, Adrenal Tumor, Secondary Hypertension, Cases Series

## Introduction

Pheochromocytoma is a tumor that originates from the chromaffin cells of the adrenal medulla in 80-85%. About 50% produce epinephrine accompanied by variable amounts of norepinephrine (adrenergic phenotype); other sympathetic pheochromocytomas or paragangliomas produce predominantly or exclusively norepinephrine (noradrenergic phenotype), sometimes with significant amounts of dopamine as the end product (dopaminergic phenotype) (Lenders *et al.*, 2020; Eisenhofer *et al.*, 2017).

Generally, sporadic tumors are diagnosed as incidentalomas, but 40% can be associated with familial disease. These patients are diagnosed at younger ages than sporadic cases and due to symptoms associated with the disease.

The estimated annual incidence in the United States of America is 5 cases per million per year. The cited prevalence varies from 0.2% to 0.6% in hypertensive patients to less than 0.05% in the general population (Eisenhofer *et al.*, 2017). National data are unavailable.

In one study, 52% were women, with a median age of 52 years at diagnosis. And the diagnosis was most frequently made as an incidental imaging finding (62%), followed by symptoms related to pheochromocytoma (Gruber *et al.*, 2019).

Male and female are equally affected (Gruber *et al.*, 2019) or a slight female predominance is observed in 50.5 to 57% (Calissendorff *et al.*, 2022).

The median age at diagnosis of pheochromocytomas-paragangliomas was between 48 and 55 years. Most present (81-89%) or single paraganglioma (7-18%), while multifocal PPGL (<1-4%) and metastatic PPGL (3-15%) are rare.

Symptoms appear in approximately 50% of cases and are generally paroxysmal. The classic triad of symptoms related to pheochromocytoma includes episodic headaches (90%), sweating (60 to 70%), and palpitations (70%). Most patients with pheochromocytoma do not have the three classic symptoms (Young *et al.*, 2022).

Another prospective study found that no single symptom was present in more than 65% of patients with pheochromocytoma (Geroula *et al.*, 2019).

About half have paroxysmal hypertension, most of the remainder have primary (essential) hypertension or are normotensive. On the other hand, patients with primary hypertension may have paroxysmal symptoms (Kim *et al.*, 2020).

The diagnosis of pheochromocytoma is made with biochemical confirmation of catecholamine hypersecretion. Both plasmatic and urinary free metabolites have near maximal negative predictive value (>99%) with similar specificity (94%) (Eisenhofer *et al.*, 2018).

The tumor should then be identified with imaging studies for its location, either with an abdominal magnetic resonance imaging (MRI) or computed tomography (CT) scan (Ahmed *et al.*, 2021). Both CT and MRI are quite sensitive (98 to 100%), but have a specificity of approximately 70% due to the higher prevalence of adrenal "incidentalomas", most of which are benign cortical adenomas (Young *et al.*, 2022).

Pheochromocytomas, regardless their malignant potential, have a similar biochemical and histologic presentation. Aggressive behavior is established by the presence of local invasion of surrounding tissues and organs (kidney, liver) or distant metastases.

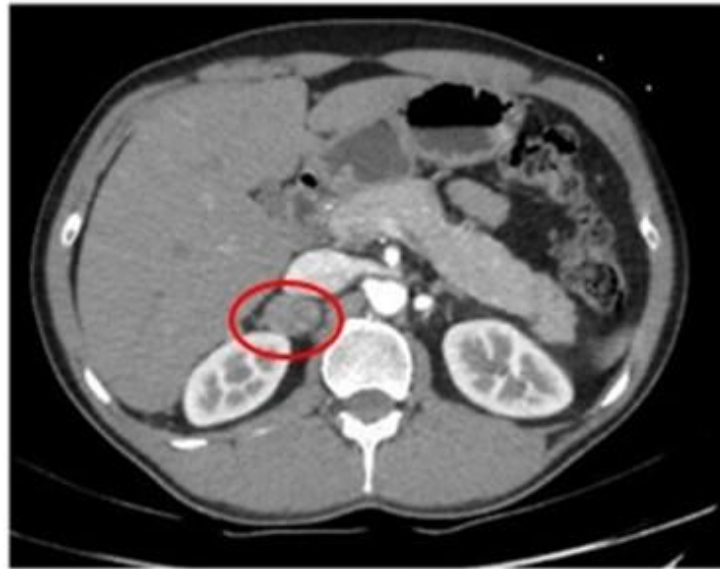
## Case Series

### Case 1

Male, 31 years old, who began in the previous 6 months with intense frontal headache, episodes of anxiety, palpitations and paroxysmal sweating. In consultation with psychiatry, anxiety disorder was diagnosed and escitalopram was started, which partial improvement. After 2 months, systolic blood pressure was greater than 200mmHg so he started enalapril firstly and then amlodipine and spironolactone due to resistant arterial hypertension. It persisted with paroxysmal episodes of palpitations and sweating, without adequate control of blood pressure. He presented no headaches or piloerection. Physical exam was normal; laboratory findings in [Table 1](#). CT: solid, well-defined nodular mass of 38x22mm in the right adrenal gland, 65% absolute wash out. (He was prepared for two weeks with terazosin 5-10 mg/day, 5 g of Na/day and normal blood pressure was achieved without  $\beta$ -blockers. Laparoscopic right adrenalectomy was performed without complications, he suffered no episodes of intraoperative or postoperative hypertension, nor hypoglycemia. The pathology reported: pheochromocytoma of 53x27x19 mm, 12 typical mitoses in HPF, Ki67 of 10%. Score 4 of the PASS scale ([Fig. 1-2](#)) (Thompson, 2002). All antihypertensive drugs were gradually descended and he remains with normal blood pressure since surgery. Urinary metanephrines in 24 hours were normal 2 months later.

**Table 1:** Values of catecholamine's in urine of Case 1 and 2.

	Normetanephrines (ug/24 hours)	Metanephrines (ug/24 hours)
<b>Case 1</b>	5886 (RV hypertensive <400)	164 (RV hypertensive < 900)
<b>Case 2</b>	1878 (RV normotensive 111-419)	8300 (RV normotensive 80-130)



**Figure 1:** Case 1. CT. Heterogeneous left adrenal tumor (red circle).



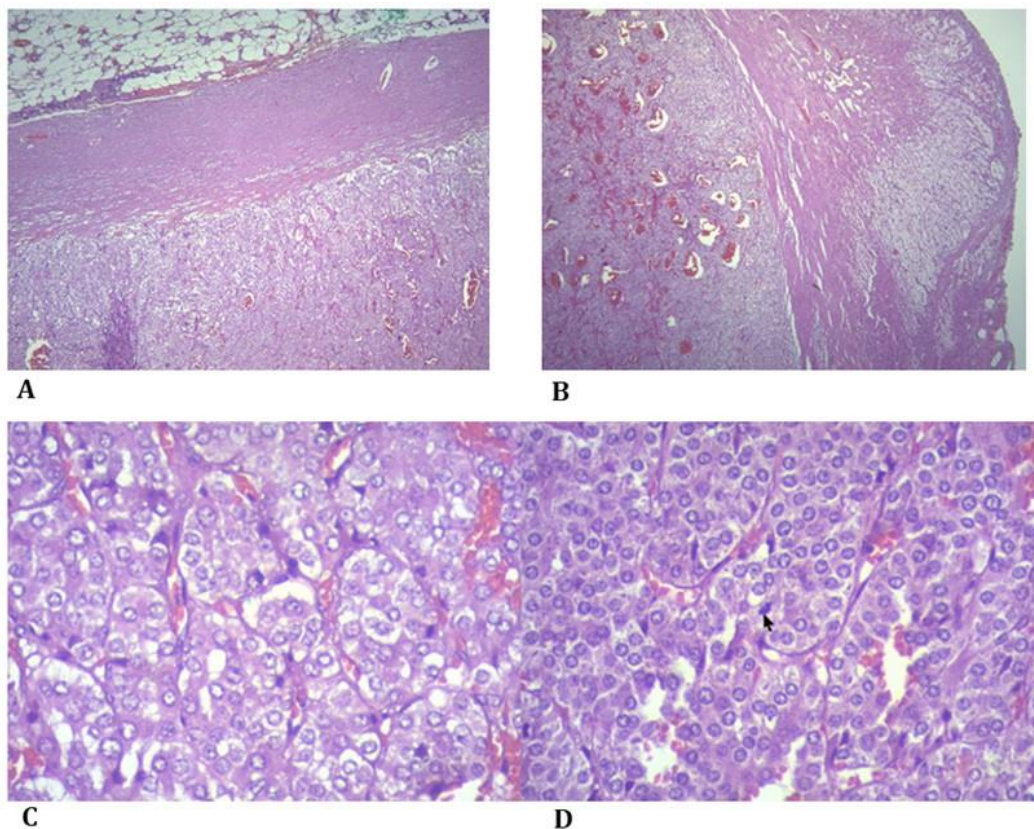
**Figure 2:** Case 1. Adrenal gland was completely extracted, macroscopic (A) and fragmented (B).

**Case 2**

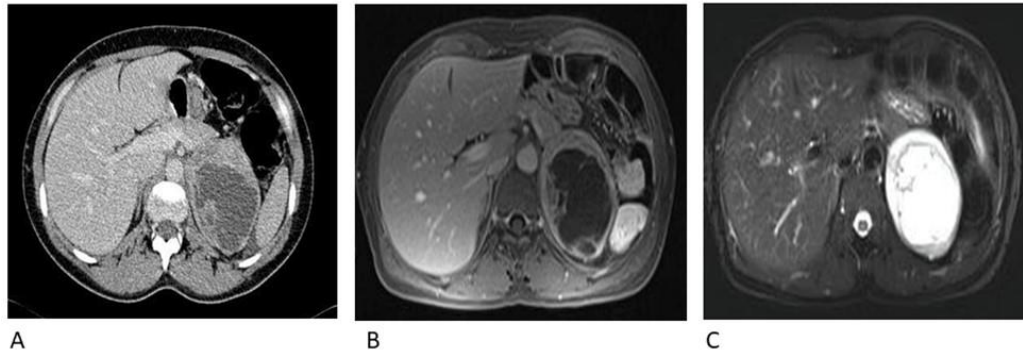
Female, 46 years old. She started in the previous 2 months with asthenia, adynamia and 10 kg weight loss that motivated the consultation. At the age of 40, she was diagnosed with chronic diarrhea and irritable bowel syndrome and treated with diet and pinaverium bromide. Hypertension of 2 years of



evolution, with poor control of blood pressure, treated with amlodipine, losartan and bisoprolol. In the last year, she presented episodes of holocranial headache, concomitantly with profuse sweating, in the morning, and intermittent palpitations for which she did not consult. On physical examination: BMI 15.4 Kg/m<sup>2</sup>. Fair general condition, thin. Cardiovascular: regular rhythm, tachycardia of 120 cpm, without elements of heart failure, blood pressure 160/90mmHg. CT was performed in order to rule out malignancy. It reported solid rounded mass, well defined borders, heterogeneous density, measuring 42 x 29 x 37 mm and showing indeterminate wash out. MRI revealed a focal lesion compatible with a pheochromocytoma of 30 x 21 x 36 mm of heterogeneous intensity, hyperintense on T2, with no elements involving adjacent structures. Catecholamines were requested in 24-hour urine (Table 1). She was prepared for 15 days with prazosin and in the immediate preoperative period she remains normotensive. Laparoscopic adrenalectomy was performed without complications and the pathology confirmed a pheochromocytoma of 44 mm in greatest diameter, with 2 mitoses per 10HPF, Ki 67 of 2%. PASS score 3 (Fig. 3-4). After a month antihypertensives were suspended and at the moment she remains normotensive.



**Figure 3:** A. Microphotography showing thick capsule in case number 1 (HEx40). B. Case 2 showed prominent vascularity with clear demarcated interphase with the cortical of the adrenal gland. C, D. Case 3 and case 4 (Hex400) showed similar histology with architecture in Zellballen.



**Figure 4:** Case 3. A. TC showing left adrenal gland mass with heterogenous density, 85x90x72mm. B. MRI (gadolinium) 10cm diameter mass contacting with kidney. C. MRI (T2) mass shows hyperintensity.

### Case 3

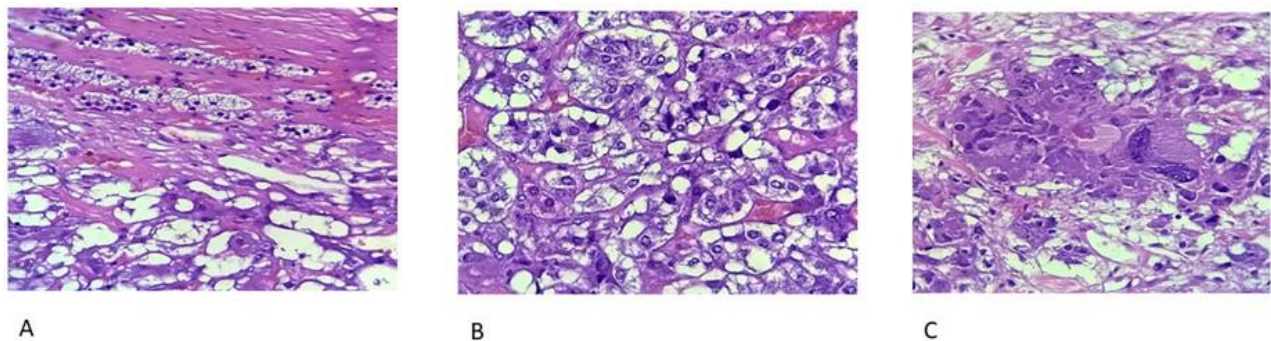
A 35-years-old female, with no history of note, who consulted for 48 hours' abdominal pain, in the flank and right hypogastrium. No digestive or urinary symptoms, no fever or elements of peritoneal irritation. The ultrasound showed a mass related to the upper pole of the left kidney, of 92 x 72mm. A CT scan revealed a well-defined, mixed, predominantly cystic, left adrenal tumor measuring 85 x 90 x 72 mm (22 Hounsfield Units). MRI showed a left adrenal tumor with a maximum diameter of 10 cm, in contact with the upper renal pole, which is displaced, and also with the pancreas, without elements of infiltration. Conclusion: Voluminous adrenal mass with characteristics of a benign lesion (Fig. 5). The patient did not present hypertension, headaches, tachycardia, or piloerection. With the diagnosis of adrenal incidentaloma, surgical treatment was proposed and a basic paraclinical test was previously requested, which was normal; catecholamines in Table 2. The corresponding preoperative preparation was performed. Blood pressure monitoring didn't show paroxysmal hypertension or hypotension. Left adrenalectomy was performed in open surgery, without complications or increases in blood pressure figures. The pathology reported a pheochromocytoma associated with a ganglioneuroma measuring 100 x 100 x 60 mm, with a multilocular cystic cavity with thin and smooth walls (Fig. 6). Adrenal gland remnant 20 x 20 mm. The Ki 67 in some sectors reached 2%, Score 2 on the PASS scale. In the evolution, the patient remained normotensive and metanephrines and normetanephrines were normal 3 months after surgery.

**Table 2:** Values of catecholamine's in urine and plasma of Cases 3 and 4.

	Urine (ug/24 hours)			Plasma (pg/ml)		
	Adrenalin (RV 0-25)	Norepinephrine (RV 0-40)	Dopamine (RV 0-300)	Adrenalin (RV 0-150)	Norepinephrine RV (105-550)	Dopamine RV (0-150)
Case 3	92	979	280	41	1209	120
Case 4	84	863	290	27	1345	94



**Figure 5:** Case 3. A. Macroscopic adrenal tumor. B. Macroscopic section with central cystic change corresponding to paraganglioma areas.



**Figure 6:** Case 3. Microphotography (HE x400) showing ganglionic cells with fibrillar (A and B) background typical of paraganglioma. This case showed typical morphology of Pheochromocytoma in the rest of the tumor (Fig C).

#### Case 4

A 34-year-old woman with a two-year history of panic attacks that did not improve with the psychotropic drugs used. No other personal clinical records. She was admitted to emergency due to a fall from his height without loss of consciousness and pain in the left flank. Abdominal tomography was performed, which reported: heterogeneous left adrenal nodule, with microcalcifications, of 36 x 28 x 30mm, 40 HU and rapid contrast washout. Catecholamine's were requested (Table 2). With the suspicion of pheochromocytoma, she was questioned again and reported episodes of piloerection, profuse sweating and palpitations, occasionally headaches, which were interpreted as panic attacks; did not present arterial hypertension. Laparoscopic left adrenalectomy was performed after surgical preparation with terazosin, remaining in normotension. During surgery, she presented a small hypertensive episode that was quickly reversed. The pathology confirms pheochromocytoma of 38 mm in greatest diameter, with 2 mitoses per 10HPF and Ki 67 of 1%. PASS score of 2 (Fig. 7). After 3 months with normal catecholamines, panic attacks are completely resolved and all psychoactive drugs are discontinued.





**Figure 7:** Case 4. Surgical piece of completely extracted adrenal mass.

## Discussion

Sustained or paroxysmal hypertension is the most common sign of pheochromocytoma, as in cases 1 and 2, but approximately 5 to 15% are normotensive. The frequency of normotension is higher in patients with adrenal incidentaloma or in those undergoing studies for familial pheochromocytoma (Gruber *et al.*, 2019). In case 3 and 4, they always maintained normotension and they presented in both cases as adrenal incidentalomas.

In the last case, the episodes of adrenergic crises were confused with panic attacks due to the similarity between the symptoms of both pathologies. They have different pathophysiological mechanism, while panic attacks are caused by a reaction to stress dependent on the central nervous system, in pheochromocytoma symptoms are produced by circulating catecholamines that depend on the sympathetic nervous system.

Headache can be mild or intense and of variable duration, it occurs in up to 90% of symptomatic patients. Headache occurred in the two symptomatic patients, which were 1 and 2. Generalized sweating occurs in up to 60% to 70% of symptomatic patients. Other symptoms include pounding palpitations, tremor, pallor, dyspnea, generalized weakness, and panic attack-like symptoms (such as cases 3 and 4) (Young *et al.*, 2022).



Sustained or paroxysmal hypertension is the most common symptom reported in approximately 95% of patients with pheochromocytoma. Other symptoms include pallor, tremors, dyspnea, generalized weakness, orthostatic hypotension, cardiomyopathy, or hyperglycemia.

Secondary causes of hypertension are generally suspected in cases of multidrug-resistant hypertension or those with sudden and early onset. As happened in both symptomatic cases here who were on at least three drugs, they remained hypertensive and normal blood pressure was only achieved preoperatively with alpha blockade.

Newly diagnosed hypertension, or hypertension associated with unexplained orthostatic hypotension, suggests an underlying pheochromocytoma, as in case 1.

A high index of suspicion is necessary during the evaluation of secondary hypertension, since untreated pheochromocytoma can cause significant morbidity and mortality, especially in patients who require surgical treatment (Kenny *et al.*, 2018).

However, about 10% of patients with pheochromocytoma are asymptomatic or mildly symptomatic (as happened in cases 3 and 4, who never had hypertension and consulted for pain, which could be due to mechanical compression generated by the large size of the tumor and incidentaloma in these cases, respectively).

Values greater than 1.5-2 times the upper limit of normality are highly suggestive of the presence of a pheochromocytoma and require further evaluation<sup>5</sup>. In all the cases presented, the values widely exceeded two or three times the upper limit and the biochemical diagnosis was made with total certainty.

Surgical resection is the only curative treatment for pheochromocytoma, but surgery itself can cause a massive release of catecholamines into the circulation; this can determine hypertensive crises, cardiac arrhythmias, myocardial infarction, pulmonary oedema and multiple organ failure. On the other hand, the rapid decrease in catecholamines after tumor resection can cause severe hypotension (Lenders *et al.*, 2020; Kim *et al.*, 2020).

To prevent these cardiovascular complications, treatment with antihypertensive drugs is recommended before surgery for at least 10 to 14 days, as occurred in all cases (Young *et al.*, 2022).

The goal of preoperative medical treatment includes BP control, tachycardia prevention, and volume expansion.

According to the clinical practice guidelines<sup>5</sup> (selective  $\alpha$ -1 doxazosin, prazosin, terazosin) should be started at least 7 days before surgery to control BP and cause vasodilation. Forty-eight hours after starting alpha blockade, a high-sodium diet (>5g/day) and increased fluid intake should be started 7 to 14 days before surgery.  $\beta$ -Adrenergic blockers (propranolol, metoprolol) should be started cautiously at a low dose and slowly titrated to control heart rate. After adequate  $\alpha$ -adrenergic blockade, usually 2 to 3 days before surgery, as early use may cause vasoconstriction in patients with pheochromocytoma. Since it is used in the presence of tachycardia and when control of BP figures is not achieved; In our cases, no patient needed it (Young *et al.*, 2022).

Multiple cases of hypertensive crisis, pulmonary oedema, cardiac arrhythmia, and cardiogenic shock have been reported in undiagnosed patients with pheochromocytoma undergoing adrenal or non-adrenal surgery who were medically unprepared with  $\alpha$  and  $\beta$  adrenergic antagonists and fluids prior to surgery (Kim *et al.*, 2020).

Most catecholamine-secreting paragangliomas are found in the abdomen and pelvis. Catecholamine secretion (Moor *et al.*, 2022). may be associated with headache and episodic hypertension and occasionally cardiovascular collapse

Minimally invasive adrenalectomy is the preferred surgical approach.

Laparoscopic and retroperitoneoscopic transabdominal adrenalectomy are the most used techniques (the former was used in the four reported patients).

The European guide recommends measurements of metanephrine, normetanephrine and 3-methoxytyramine two to six weeks after recovery from surgery depending on the nature of the elevated concentrations before surgery (Plouin *et al.*, 2016).

There is consensus that all patients should be followed up during the first ten years after surgery (Lenders *et al.*, 2020).

Patients with large tumors, paragangliomas have a high risk of metastatic progression (Moor *et al.*, 2022; Pamporaki *et al.*, 2017).

On the other hand, the PASS score is a pathology scale that adds prognostic elements and establishes a score that is used to predict metastasis. PASS score <4: suggests low risk of metastasis and  $\geq 4$  high risk; with a sensitivity of 50% and specificity of 45% (Thompson *et al.*, 2021).

In addition, pheochromocytoma larger than 4 cm require higher doses of  $\alpha$ -adrenergic blockade and have a longer hospital stay, demonstrating the importance of proper preparation for surgical planning (Gruber *et al.*, 2019).

The 5-year survival rate for metastatic PPGLs was 84%. Individualized treatment is required for malignant pheochromocytoma and paragangliomas (Kim *et al.*, 2020). However, some studies suggest that survival for pheochromocytoma is improving in recent years, perhaps related to earlier diagnosis using case detection tests and incidental imaging findings (Gruber *et al.*, 2019).

## Conclusions

The clinical presentation of these tumors can be very uneven, care must be taken to make an early diagnosis, adequate preoperative preparation to avoid surgical and postoperative complications and thus reduce the morbidity and mortality of this disease. Only 5–15% of pheochromocytomas are normotensive within adrenal incidentalomas and occur mainly in large cystic tumors (Mintegui *et al.*, 2022).

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