Pheochromocytoma: Three clinical case reports

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Abstract

Pheochromocytomas are rare neuroendocrine tumors with a highly variable clinical presentation, the most common presentations being episodes of headaches, sweating, palpitations and hypertension. The serious and potentially lethal cardiovascular complications of these tumors are due to the potent effects of secreted catecholamines. Biochemical testing for pheochromocytoma is indicated, not only in symptomatic patients, but also in patients with adrenal incidentalomas or identified genetic predispositions (multiple endocrine neoplasia type 2, Von Hippel Lindau Syndrome, neurofibromatosis type 1).

The authors report three cases in which a biochemical diagnosis of pheochromocytoma was made: the first is that of a 30 year-old man admitted for investigation of a right adrenal 6cm diameter incidentaloma; the second is a 35 year-old woman studied for secondary hypertension, and the third is a 59 year-old woman, otherwise healthy, with a right supra-renal node on a routine ultrasound exam. Imaging techniques such as CT, MRI, and functional ligands such as (123) I-MIBG were used to localize the biochemically proven tumor.

After the use of appropriate preoperative treatment to block the effects of secreted catecholamines, laparoscopic tumor removal was the preferred procedure.

Prognosis is excellent.

Key words: pheochromocytoma, hypertension, metanephrines.

Introduction

Pheochromocytomas are rare neuroendocrine tumors that produce catecholamines, with an estimated incidence of 2 to 8 cases per million people, annually.[1,2] Its main clinical symptom is arterial hypertension, either constant or intermittent, generally associated with paroxystic symptoms. Pheochromocytoma should also be considered if a patient has labile arterial hypertension, hypertension which is resistant to antihypertensive therapy, or paroxystic symptoms.[3-7]

The correct diagnosis is important, as resection of the tumor reverts the clinical symptoms and cures hypertension. Delay, or failure to make the correct diagnosis, can cause considerable morbidity and mortality.[8,9]

Clinical case nº 1

A 30-year old individual with irrelevant personal antecedents, who was admitted to the HFF Emergency Service with non-specific abdominal pain, but no other accompanying symptoms; the patient underwent abdominal echography, which revealed a right suprarenal nodule approximately 6 cm in diameter, and was admitted to the Medicine Service for study.

Objective examination without alterations.

From the analytical study carried out, plasma catecholamines are highlighted: adrenalin «20 pg/mL (« 150), NAD 759 pg/mL (« 370), dopamine «20 pg/mL (« 200); Catecholamines (24-hour urine): adrenalin 6 ug/24h (« 18), NAD 208 ug/24h (« 55), dopamine 113 ug/24h (« 400); vanilmandelic acid – HPLC (24-hour urine): 14.6 mg/24 h (« 13.6); total plasma metanephrines 3746 (700 pg/mL); plasma normetheneprine 3575 (300 pg/ml); plasma cortisol 7.24 ug/dL (4,3- 22,40); ACTH 47 pg/mL (6-76 pg/mL); PTH 28,90 ug/dL; prolactin 16,5 ug/dL; Calcitonin «5 ug/dL.

Electrocardiogram, teleradiography, echocardiogram, ambulatory blood pressure monitor (ABPM), thyroid function, viral serologies and thyroid echography were requested, and did not reveal any alterations.

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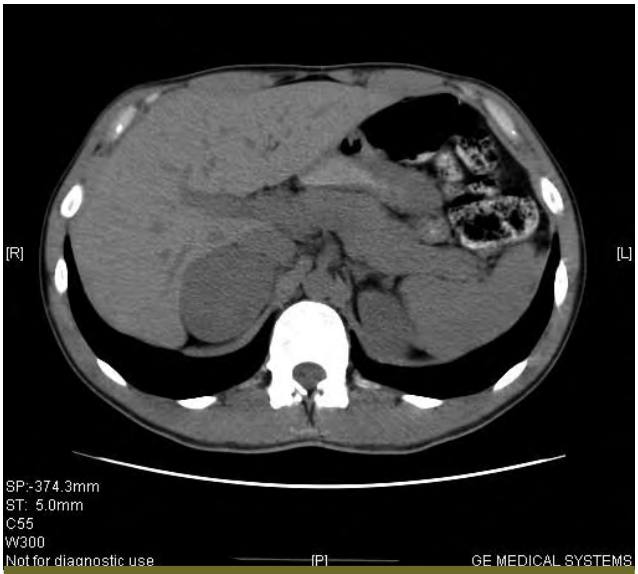
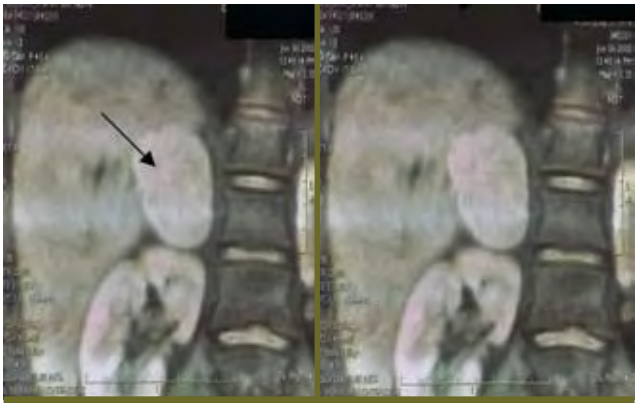


CT image of right suprarenal nodule of 6 cm in diameter.

FIG. 1



MRI image of voluminous right suprarenal mass of 6 cm in diameter, with well-defined limits and preservation of the cleavage plane.

FIG. 2

To better characterize the suprarenal nodule, and due to a positive diagnosis of Pheochromocytoma, the patient was submitted to abdominal CT and MRI *(Fig.1 and 2)*, as well as I-IMBG scintigraphy *(Fig.3)*, for localization of the tumor and exclusion of multifocal disease (scintigraphy), which revealed a right suprarenal nodule of approximately 6 cm in diameter.

A preoperative block was performed with phenoxybenzamine 10 mg, twice daily, increasing the dose by 10-20 mg every 2-3 days, up to a daily maximum dose of 1mg/kg.

After prior contact with the Anesthesiology service and ensuring a place in intensive care, surgical intervention was scheduled with the Urology sector. Surgery was performed by laparoscopy, extracting the encapsulated nodule *(Fig.4)*. The procedure was carried out without complications.

The anatomical-pathological diagnosis of Pheochromocytoma *(Fig.5 and 6)*.

Post-operative without complications, patient was discharged in good condition.

Catecholamine, metanephrine and VMA levels within the normal limits (postoperative).

Clinical case nº 2

A 25-year-old woman who was referred to an external Medical appointment with high blood pressure (AT-140/105 mmHg) and headaches, to exclude a secondary cause of AHT. No other accompanying symptoms.

Objective examination without alterations.

From the analytical study, catecholamines are highlighted (24-hour urine): total – 715 mcg/24 h (« 575), adrenaline – 14 mcg/24h (« 20), NAD – 475 mcg/24h (« 105), dopamine – 289 mcg/24h (« 450), vanilmandelic acid (24-hour urine) 8.0 mg/24 h (« 6.7).

Before the clinical suspicion and the biochemical diagnosis of Pheochromocytoma, abdominal CT and MRI were requested, as well as a I-IMBG scintigraphy for localization of the tumor and exclusion of multifocal disease, revealing a left suprarenal nodule of 2.2 cm in diameter.

Postoperative blocking was carried out with phenoxybenzamine 10 mg twice daily, increasing the dose by 10-20 mg every 2-3 days, up to a daily maximum dose of 1mg/kg.

Surgical intervention via laparoscopy occurred without complications.

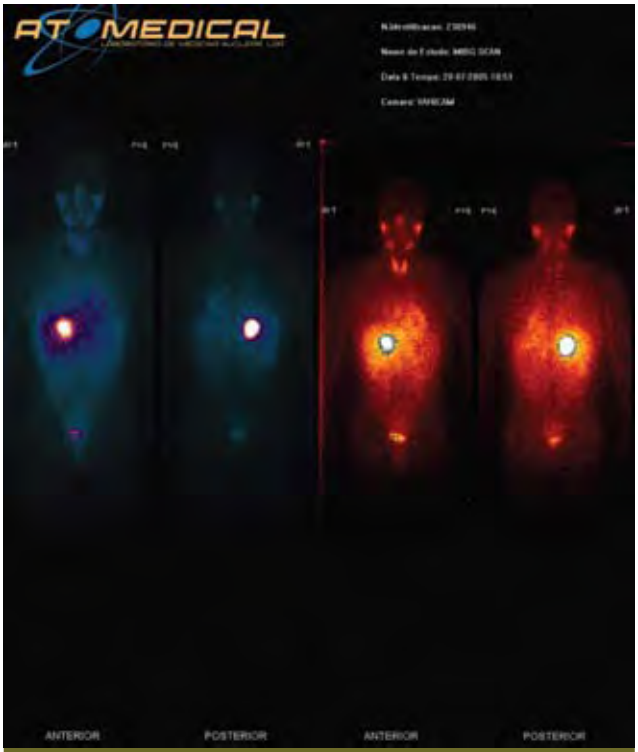
Anatomical-pathological diagnosis of Pheochromocytoma.

Postoperative without complications, patient was discharged in good condition.

Catecholamine and VMA levels within the normal limits (postoperative).

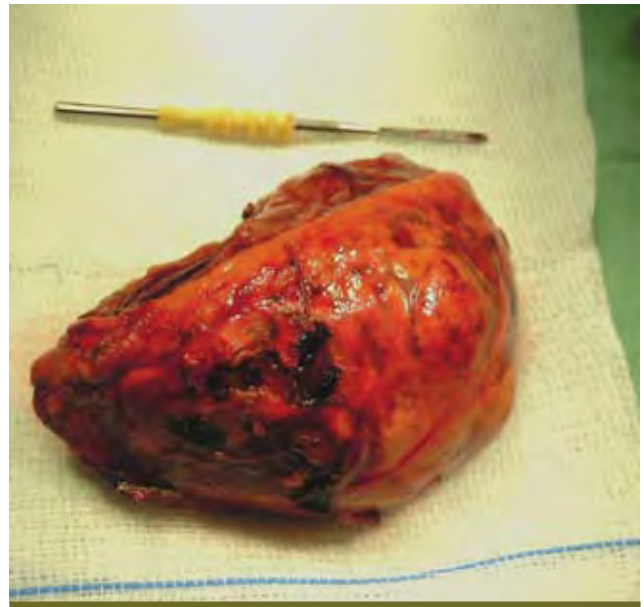
Clinical case nº 3

A 59-year-old woman, hypertensive for around 5 years



MIBG scintigraphy– hyperfixing voluminous mass projected in the area of the right suprarenal gland, corresponding to a large Pheochromocytoma.

FIG. 3



Encapsulated nodule of 75 gr 7*5*4.5 cm.

FIG. 4

(TA-180/110 mmHg), controlled with a drug of the ARA II group which was prescribed by the assistant doctor at an external General Surgery clinic, revealing, in a routine echography requested following investigation of a hematuria, a right suprarenal nodule around 3 cm of greater diameter, confirmed in CT of the suprarenals.

In this context, the patient was subsequently referred to the external Internal Medicine clinic, to rule out a probable Pheochromocytoma.

Objective examination without alterations.

In the analytical study carried out, plasma catecholamines are highlighted: adrenaline 586 pg/mL (« 150), NAD 1275 pg/mL (« 370), dopamine «20 pg/mL (« 200); catecholamines (24-hour urine): adrenaline – 197 mcg/24h (« 55), NAD – 72 mcg/24h (« 18), dopamine – 215 mcg/24h (« 400); vanilmandelic acid (24-hour urine) : 12,10 mg/24 h (« 13,60); plasma metanephrine 108 (« 90 pg/mL); plasma normetanephrine 911 («200 pg/mL); urinary metanephrine 1128 (74-297 pg/mL); urinary normetanephrine 1612 (105-354 pg/mL); aldosterone – 66.1 pg/mL (35-275); cortisol – 21.3 ug/dL (4,3- 22,40); basal ACTH– 6.29 pg/mL (« 46).

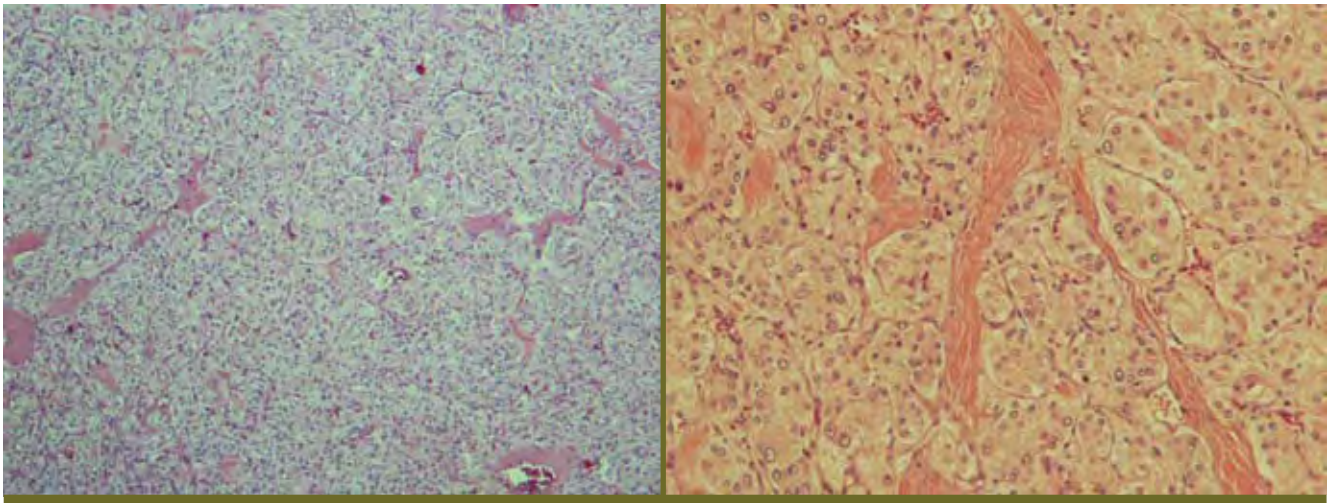
Due to clinical suspicion and the biochemical diagnosis of Pheochromocytoma, a CT was requested, which revealed "…increase in volume of the right suprarenal gland, in which a nodular formation was observed, 29 mm in diameter with solid density, and clearly kept contrast …" and abdominal MRI with "… nodular formation at the convergence of the stems of the right suprarenal gland; measures 30x23x36 mm in diameters AP, T and L respectively…the characteristics described should form part of the clinical context, and are suggestive of a Pheochromocytoma". I-IMBG scintigraphy was also requested, for localization of the tumor and exclusion of multifocal disease, which was negative for evidence of Pheochromocytoma of the right suprarenal gland.

Preoperative block was performed with phenoxybenzamine at 40 mg daily, associated with βblocker with propranolol 20 mg 8/8h.

Surgical intervention by laparoscopy was performed without complications.

Anatomical-pathological diagnosis of Pheochromocytoma.

Postoperative without complications, patient was



HE X 10.

FIG. 5

discharged in good condition.

Catecholamine, metanephrine and VME levels within the normal limits (postoperative).

Discussion

Pheochromocytomas are rare neuroendocrine tumors which produce catecholamines originating in the chromaffin cells; they are mainly found in the suprarenal medulla (80-85%), although in 15-20% of cases, they develop from chromaffin tissue outside the suprarenal (adjacent to the sympathetic ganglions of the neck, mediastine, abdomen and pelvis) and are commonly known as paragangliomas.[1,2]

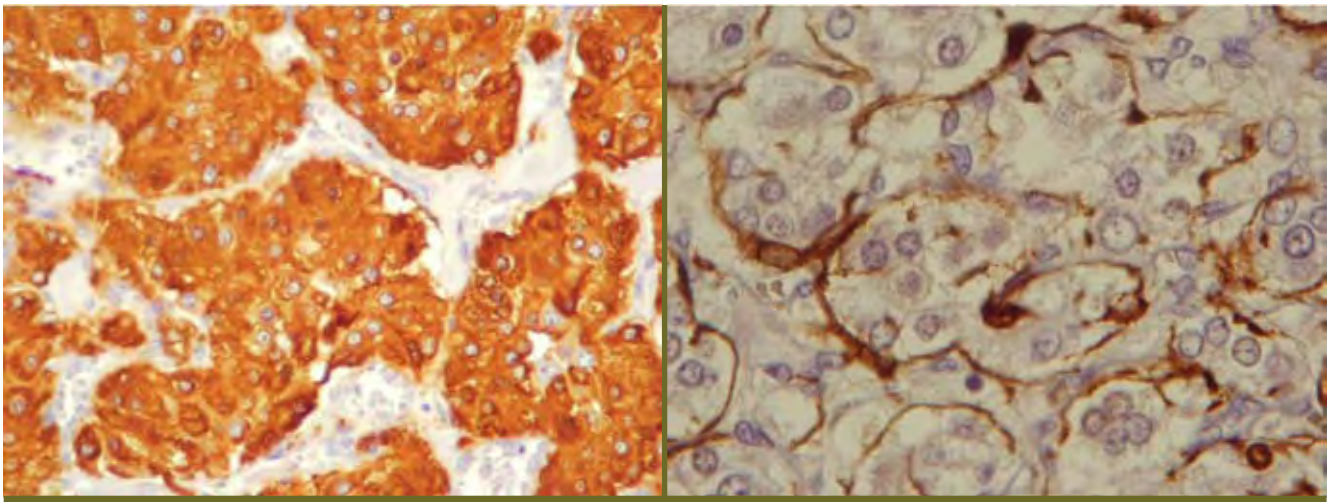
There is a prevalence of 0.1-0.6% in patients with arterial hypertension (AHT) and 0.05% in autopsy, which indicates that the majority of tumors go unnoticed, resulting in premature mortality. These tumors are lethal when not diagnosed and treated, but are cured in the majority of patients, if diagnosed early.[3-9]

Hereditary pheochromocytomas, generally diagnosed in individuals aged under 40 years, occur in type 2 multiple endocrine neoplasia (MEN), in Von Hippel Lindau syndrome, in type 1 neurofibromatosis (NF-1) and in cases where there is a family history of paragangliomas[10,11]; the sporadic forms are generally diagnosed in individuals aged 40-50 years[12-14]. Pheochromocytoma is rare in children, but where it does exist, it generally originates outside the suprarenal, is multifocal and is associated with hereditary syndromes.[15-16]

The clinical presentation is highly variable; the vast majority of signs and symptoms are due to the direct effect of the released catecholamines: AHT, palpitations, pallor, headaches, and sweating. Despite the non-specificity of the symptoms, the simultaneous presence of headaches, palpitations and sweating increases the probability of this diagnosis by more than 90%.[17] The metabolic effects include hyperglycemia, lactic acidosis and weight loss.[18]

AHT is generally paroxystic, occurring in certain individuals with a stable AHT base, while others have normotensive values between paroxysms. On the other hand, arterial tension may be consistently normal, especially in patients with suprarenal incidentalomas, identified family syndromes, or tumor of small proportions.[19] The number of normotensive and asymptomatic patients diagnosed with this disease has risen steadily. Around 5% of all incidentalomas are Pheochromocytomas, with 25% of all Pheochromocytomas being discovered accidentally during imaging studies carried out for other reasons.[20-24]

Paroxysm of the signs and symptoms, secondary to episodic secretion of catecholamines, increases the diagnostic probability of these tumors. The anesthetic procedures and the handling of the tumors are important catecholaminergic stimuli; food, drugs or chemical compounds (radiographic contrast products,



Chromogranin and S-100.

FIG. 6

methoclopramide, and anticyclic antidepressants) can also induce paroxysms. The clinical condition is unpredictable, and can last from several minutes to approximately 1 hour. Despite this, a delay of 3 years is still seen between the onset of symptoms and the final diagnosis.[25-26]

Thus, biochemical study of Pheochromocytomas is indicated, not only in symptomatic individuals, but also in those with suprarenal incidentalomas (suprarenal tumors detected through imaging methods carried out for reasons not related to the suprarenal dysfunction, the majority of which are benign and inactive from a hormonal point of view) or identified genetic predispositions.[27] The traditional biochemical tests include measurement of the plasma and urinary catecholamines, urinary vanilmandelic acid (VMA), urinary and plasma metanephrines (normetanephrine and metanephrine); recent studies suggest that the measurement of the urinary and plasma metanephrines is the most sensitive diagnostic test, and therefore the most reliable, if negative, for the exclusion of Pheochromocytoma. Therefore, drugs that interfere with these medications, leading to false positive results, should be suspended (phenoxybenzamine, tricyclic antidepressants, beta-blockers, Levodopa, drugs containing catecholamines, ethanol, and stress factors such as infarction and/or obstructive sleep apnea).[28]

To localize the biochemically diagnosed tumors, imaging methods are used, such as CT or MRI (children and pregnant women) and functional ligands such as ^{123}I-MIBG scintigraphy (negative CT or MRI). If the ^{123}I-MIBG scintigraphy is negative, positron emission tomography (PET) studies are performed with specific ligands [18F] DA and [18F] DOPA; if these are also negative, the patient probably has a rare type of Pheochromocytoma (the tumor cells do not express norepinephrine, or have a small number of catecholamine secreting granules) or a malignant Pheochromocytoma.[29]

The use of appropriate preoperative treatment to block the effect of the segregated catecholamines has decreased perioperative mortality to less than 3%.[30] The objective is to prevent potential serious complications induced by the catecholamines during surgery, notably hypertensive crises, arrhythmias, acute pulmonary edema and myocardial ischemia [31] Thus, preoperative stabilization and scheduling before an elective surgical intervention is always preferable.[32] There have been no randomized trials large enough to establish which is the most effective drug before surgery. Traditional schemes include phenoxybenzamine, prazosin and doxazosin.[33] Phenoxybenzamine is the preferred drug, as it blocks the α-receptors in a non-competitive way.[34] Other alternative drugs include labetalol (which, being an α and β blocker, with greater action in the latter, is not so effective) or the blockers of the calcium channels of the group

of dihydropiridines (which, although they do not cause orthostatic hypotension *per se*, are not sufficient to avoid hemodynamic instability).[35] Another drug that can be used in this perioperative period is metyrosine, and although two retrospective studies have demonstrated that in association with phenoxybenzamine there is less need for antihypertensive drugs during surgery, no prospective study has been carried out.[36]

The treatment lasts, on average, 10 to 14 days. The initial dose of phenoxybenzamine is 10 mg, twice daily, increasing by 10-20 mg every 2-3 days, up to a maximum daily dose of 1mg/kg (sufficient in the majority of patients. A beta-blocking agent (propanolol 40 mg three times daily, or atenolol 25-50 mg daily) may be associated only after several days of α blocking, particularly in patients with associated tachyarrythmias.[37]

To ensure adequate preparation, various criteria have been proposed:

• Decrease in arterial tension (AT) to below 160/90 mmHg for at least 24 hours;

• Orthostatic hypotension should be present, but supine AT should not be less than 80/45 mmHg;

• No more than one ventricular extrasystole every 5 minutes;

• Electrocardiogram without alterations of the S-T segment and T-wave inversions for one week;

The complications that could occur during surgery are:

• Hypotension (resolved with an increase in salt and liquid intake);

• Hypertensive crises (control with bolus dose or continual infusion of phentolamine, sodium nitroprussiate or nicardipine);

• Tachyarrhythmias (infusion of short-action β blocker);

The postoperative period (at least the first 24 hours) should take place in an Intensive Care Unit, paying special attention to situations of hypotension (due to an abrupt drop in circulating catecholamines following removal of the tumor, and the presence of phenoxybenzamine) resolved through the replacement of fluids, and occasionally, endovenous or vasopressin ephedrine (if the latter drug is ineffective) and hypoglycemia (caused by rebound hyperinsulinemia due to the recovery of insulin release after removal of the tumor).[38]

Removal of the tumor by laparoscopic surgery is the preferred surgical method, decreasing postoperative morbidity, length of time in hospital, and costs. It has a mortality rate of 1%, morbidity of 8% and conversion rate of less than 5%.[39]

Follow-up should be annual, during the first 10 years after surgery, and indefinitely if there is positive family history, or in the presence of paragangliomas.

The prognosis, unlike that of patients with metastases (large tumors, paragangliomas), is generally excellent.[40]

Thus, due to the rarity of these tumors and the wide variability of their clinical presentation, the authors present these three clinical cases relating to patients investigated by the Medicine Service of our hospital, in which a biochemical diagnosis of Pheochromocytoma was made: two patients aged 30 and 59 years, admitted for investigation of suprarenal incidentalomas, and a third case of a young person aged 25 currently undergoing study for a secondary cause of arterial hypertension.

In almost all these cases, imaging methods were used, such as computerized tomography, nuclear magnetic resonance and scintigraphy I-MIBG (123) for localization the tumors, followed by appropriate preoperative therapy to block the effects of the released catecholamines, the patients were submitted to laparoscopy, which was carried out without complications. Catecholamine, metanephrine and VMA levels within the normal limits (postoperative). ■

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