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CASE

Association of Adrenal Medullar and Cortical Nodular Hyperplasia

A Report of Two Cases with Clinical and Morpho-Functional Considerations

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Arterial hypertension of adrenal etiology is mainly attributed to primary hyperaldosteronism. However, subtle expressions of hyperadrenergic or glucocorticoid excess can also generate arterial hypertension. The present report describes two hypertensive patients cataloged as resistant essential hypertensives, in whom adrenal masses were found incidentally, who highlight the need to recognize these tenuous clinical or laboratory presentations. Case 1 was a 50-yr-old female with hyperadrenergic hypertension associated to a left adrenal node, normal cortisol and aldosterone:renin ratio, marginally increased urinary normetanephrine, and a positive ^{131}I MIBG radioisotope scan. Adrenalectomy normalized blood pressure and urinary metanephrines. Pathology showed a hyperplastic adrenal medulla associated to a multinodular cortical hyperplasia. Case 2 was a 62-yr-old female with progressive hypertension, a slight Cushing phenotype, non-suppressible hypercortisolism, normal urinary metanephrines, and bilateral adrenal nodes. Bilateral adrenalectomy and subsequent replacement normalized blood pressure and phenotypic stigmata. Pathology demonstrated bilateral cortical multinodular hyperplasia and medullary hyperplasia. The clinical study in both patients was negative for MEN. The apparently rare association of cortical and medullary lesions presented by both patients is probably overlooked in routine pathology exams, but should be meticulously searched since the crosstalk between the adrenal cortex and medulla may prompt dual abnormalities.

Key Words: Hyperadrenergic hypertension; glucocorticoid hypertension; adrenal medullar hyperplasia; adrenal cortical adenoma; pheochromocytoma; incidentalomas.

Introduction

The prevalence of secondary hypertension continues to be low, in spite of the advent of biochemical and imaging diagnostic tests *(1)*, with the exception of primary aldosteronism, which has shown an increase due to the use of the aldosterone:renin ratio *(2)*. The frequent detection of adrenal tumors due to the massive use of imaging techniques, the necropsy findings of tumors undetected in vivo, and the increasing demonstration of familial syndromes point to an underdiagnosis of adrenal functional lesions *(3,4)*. The clinical relevance of failing to characterize adrenal secondary hypertension derives in resistant hypertension, in unrecognized neoplasias, which might progress undetected to the metastatic stage, and in the case of genetic mutations to a missed diagnosis of the adrenal lesions/enzymatic defects and their associated syndromes in the index case and in his kindred.

With the intention of contributing to increase our clinical sensitivity, we describe two cases that presented with subtle characteristics of adrenal hypertension. Their secondary hypertension presented according to the predominant hormonal/anatomical derangement, and hypertension remitted after surgical resection of the abnormal adrenals. In spite of symptoms of adrenergic hypertension and of the slight Cushingoid phenotype, both patients had been managed as essential hypertensives and cataloged as resistant, and the diagnosis were done retrospectively after detecting incidental adrenal lesions by images requested because of non-specific symptoms. Moreover, both patients displayed an association of cortical and medullary lesions, an association that should probably be more frequently found due to the important functional interaction between cortex and medulla *(5,6)*.

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Case Reports

Case 1

A 50-yr-old Hispanic female presented for 6 mo prior to admission with resistant variable hypertension, severe headaches, tachycardia, flushing, profuse sweating, and irritability. She had a chronic severe constipation, a long-standing depression, and recurrent benign mammary nodes. She was amenorrheic for 1 yr. Her father died at 48 yr of a cerebellar tumor that presented at 30 yr, her 84-yr-old mother was hypertensive, one of two brothers had a seminoma, and three of her five siblings presented cutaneous myxomas, one a café-au-lait spot.

An abdominal CT scan, performed because of severe right subcostal pain, showed a 1.2 cm left adrenal node, a 6 × 4.9 cm hepatic cyst, bilateral renal cysts of 3 and 2.1 cm, and a normal pancreas (Fig. 1A). On admission we found an obese (BMI 31 kg/m^2), sweaty patient, with a blood pressure of 162/94, 161/104, and 185/109 mmHg in the lying, sitting, and standing position, with heart rates of 104, 98, and 96 bpm, respectively, while receiving losartan 50 mg daily. Multiple pediculated and flat lentigos were present in the lower part of face and in neck (Fig. 1B). The rest of the physical exam was negative.

Her laboratory work-up, detailed in Table 1, demonstrated urinary metanephrines between the ranges of the normotensive population and the pheochromocytoma patients. An echocardiogram revealed left ventricular hypertrophy, and no valvular dysfunction or lesions. An ^{131}I MIBG scan performed 48 h after radioisotope administration showed a faint area of radioactivity in the left adrenal area (Fig. 1C).

With the diagnosis of pheochromocytoma, the patient was started on doxazocine, to which atenolol was latter added, achieving control of her blood pressure with 3.0 and 37.5 mg daily, respectively. Treatment was maintained for 1 mo, during which persistent normotension was confirmed.

The patient was submitted to an open left adrenalectomy, during which she maintained normotension, with the exception of a systolic of 200 mmHg associated to palpation of the left adrenal tumor. She had a normotensive postoperative period and was discharged at the sixth postoperative day.

On the 17th postoperative day urinary metanephrine was 69 μg/24 h and normetanephrine 332 μg/24 h. A neck echography did not reveal thyroid or parathyroid nodes, and the serum PTH and calcitonin levels were 59.5 and <5.0 pg/mL, respectively.

The adrenal biopsy (Fig. 1D) showed a gland of 4 × 2.2 × 1.5 cm, weighing 7.4 g, with multiple cortical nodules, the larger being 12 mm of diameter, and the remaining 2–8 mm. In addition, the cortical layer presented myelolipomatous metaplasia. After excluding the nodules by microdissection, the adrenal gland weighed 3.622 g and the medulla 0.913 g, corresponding to 25% of the non-nodular gland (10% in a normal 4–6 g adrenal gland). Light microscopy showed a cortical multinodular hyperplasia and a hyperplasia of the medulla. Cortical nodes were composed of clear lipid-rich cells (Fig. 1D inset). Chromogranin (Fig. 1E) and synaptophysin were both positive for the adrenal medulla, while enolase staining was negative. The chromogranin-positive zones showed an irregular festooned pattern in its limit with the cortex, in parts of the periadrenal fibroadipose tissue, and in some areas of the surrounding veins. The medullar ultrastructure showed predominantly epinephrine granules of 140 nm diameter (Fig. 1F).

Six months after surgery the patient had a blood pressure of 134/64 and 123/68 mmHg lying and standing, respectively, with no headaches, flushing, or sweating. Urinary metanephrine was 47 μg/24 h, and normetanephrine 219 μg/24 h.

Case 2

A 62-yr-old female of Slavic descent presented with a hypertension of 10 yr duration, which increased progressively during the 7 mo prior to admission. During this period she noted facial plethora, easy bruising, and diminished strength. She had a toxic multinodular goiter 5 yr previous, which failed to respond to radioiodine, and required thyroidectomy; the biopsy showed a follicular nodular hyperplasia. Her mother died at 86 yr of a cerebral tumor and her father died at 64 yr of a lung cancer, but none of her seven siblings had a neoplasia.

A thorax CT scan, performed because of chest discomfort, showed a right adrenal nodule, suggestive of adenoma. A MRI confirmed adrenal nodules of 2.6 cm and 2.7 cm at right and left, respectively (Fig 2A). In the physical examination she had a blood pressure of 140/90 mmHg lying, on atenolol 25 mg, enalapril 20 mg, and hydrochlorothiazide 12.5 mg per day, centripetal adiposity within a normal BMI of 25 kg/m^2, a terse, slightly puffy face (Fig. 2B), bruises in arms and legs, and decreased strength involving the shoulder girdle and lower limbs. She presented no hirsutism, lentigines, café-au-lait spots, or cutaneous myxomas.

Her laboratory work-up, detailed in Table 1, demonstrated serum potassium in the lower normal limit, a suppressed plasma renin activity, a high urinary free cortisol (F), and normal urinary metanephrines. Overnight low- and high-dose dexamethasone tests demonstrated persistent high cortisol values (Table 2), and a basal ACTH < 5.0 pg/mL confirmed the diagnosis of an adrenocorticotropic hormone-independent Cushing syndrome.

A bilateral laparoscopic adrenalectomy was performed. The adrenal biopsy showed a right adrenal gland of 6 × 2.2 × 2.4 cm, weighing 13.5 g, and a left adrenal gland of 6 × 2 × 1.8 cm weighing 13.7 g, both with multiple cortical nodules, the larger being 3.0 cm in diameter (Fig. 2C). After excluding the nodules by microdissection, the right adrenal gland weighed 3.1 g and the medulla 0.98 g, while the left weighed 3.6 g and the medulla 1.3 g, thus corresponding to 31% and 35% of the non-nodular right and left glands, respectively. Light microscopy showed bilateral cortical multinodular hyperplasia, and the medulla presented

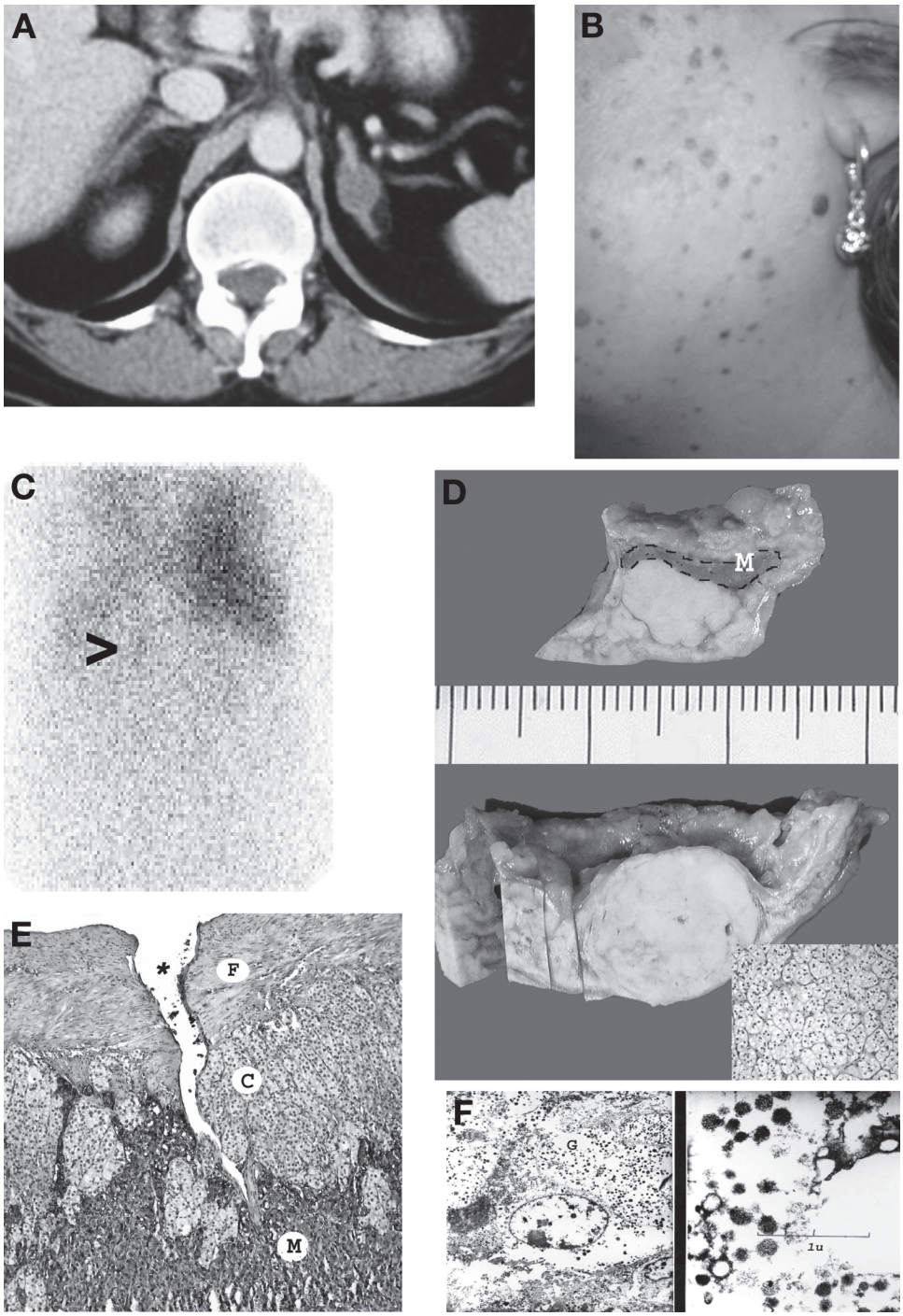

Fig. 1. (**A**) Section of abdominal tomography showing a 1 × 1 cm node in the left adrenal gland. (**B**) Abundant pediculated and flat lentigos in the lower part of face and neck. (**C**) Uptake of MIBG in the area of the left adrenal. (**D**) Upper panel: Adrenal cortex with several yellow nodes. M=adrenal medulla limited by the discontinuous line. Lower panel: Cortical 12 mm node. Inset: Clear cell node in the adrenal cortex (HE, ×200). (**E**) Chromogranin staining shows a festooned and irregular limit between the adrenal cortex (C) and medulla (M). Medulla attains in sections the fibrous capsule of the adrenal (F). (*) vein. (×100). (**F**) Numerous cytoplasmic chromogranin granules (electron microscopy, ×25,000) at left. Characteristic epinephrine granules of approximately 140 nm diameter (electron microscopy, ×60,000) at right.

hyperplasia in the non-nodular cortical areas (Fig. 2D). Cortical nodes were composed of clear cortical cells. Chromogranin-positive cells within the non-nodular cortical zone were poorly limited, and presented in isolation, as streamers or as clusters (Fig. 2E).

The patient was discharged on the fifth postoperative day on hydrocortisone 30 mg, fludrocortisone 0.05 mg, and L-thyroxin 75 µg daily, and on no antihypertensive therapy. One month after the adrenalectomy her blood pressure was 145/72 and 133/70 mmHg lying and standing, respectively,

Table 1
Laboratory Work-up in Patients 1 and 2

	Case 1	Case 2
Hematocrit (%)	42	44
Glucose (mg/dL)	100	94
Cholesterol (mg/dL)	185	197
Creatinine (mg/dL)	0.8	0.9
Sodium/potassium (mmol/L)	140/3.9	145/3.6
Plasma renin activity (ng/mL/h)	3.3	0.2
Plasma aldosterone (ng/dL)	13.8	8.6
Urinary metanephrine (μg/24 h)	152	83
Urinary normetanephrine (μg/24 h)	634	152
Cortisol (μg/dL)	16	17.6
TSH (μg/dL)	3.75	1.35
Urinary free cortisol (F) (μg/24 h)	ND	314
DHEAS (μg/mL)	ND	0.63

ND = Not determined

and her heart rate was 70 bpm. She had lost 7 kg, her facial puffiness had regressed (Fig. 2F), her muscle strength recovered, and her serum sodium and potassium values were 143 and 4.2 mEq/L, respectively.

Discussion

These two hypertensive patients with an association of cortical and medullary adrenal hyperplasia, presenting at our hospital within 6 mo of each other, underscore the need to increase the clinical sensitivity to subtle clinical or laboratory forms of adrenal hypertension. In addition, these two cases support the notion that the adrenal medulla and the fasciculata present a range of functional alterations—spanning between biochemical alterations to the classical full fledged clinical expressions—similar to those reported for the zona glomerulosa originating the different forms of primary aldosteronism *(2)*.

Hypertension secondary to pheochromocytoma, or extraadrenal chromaffin tumors, is considered to occur in less than 1% of hypertensives *(1)*. However, the increased detection by genetic testing, imaging procedures, or necropsy studies point to a more frequent occurrence *(3,4)*. In addition, adrenal medullary hyperplasia, up to now a biopsy finding in patients suspected of pheochromocytoma, should be considered a diagnostic entity in patients with overt or subtle hyperadrenergic syndrome, normal adrenal imaging, and/or borderline increases of catecholamines or their derivatives. To increase our sensibility to variants of autonomous hyperadrenergic hypertension, we must be aware that the upper range of reference values (Table 3) vary according to age and sex, and that a grey zone exists between the values obtained in normotensive subjects and patients with pheochromocytoma, which probably includes hypertension due medullary hyperplasia.

Adrenal medullary hyperplasia, described as rare, was conclusively documented as a distinct clinical entity, and a curable cause of hypertension by Montalbano in 1962 *(7)*, and was reported within the MEN2 complex by Carney et al. in 1976 *(8)*. Cases of sporadic medullar hyperplasia have also been reported *(9–12)*. Carney and DeLellis *(8,13)* suggest that the diffuse hyperplasia of the adrenal medulla would later lead to multifocal nodes, and in its final stage a pheochromocytoma. However, a diffuse hyperplasia need not be a prerequisite for the development of nodules, because medullary nodes have been found in its absence. In case 1 the multiple facial and neck lentigos, the hepatic and renal cysts, and cerebellar and a testicular tumor in father and brother respectively pose the possibility of a familial syndrome within the spectrum of inheritable neuro-cutaneous or endocrine syndromes due to mutations in tumor suppressor genes, most probably the Carney complex *(14)*.

Hypertension due to hypercortisolism is also considered a rare entity, but due to its phenotypic characteristics is included within the easily diagnosed causes of secondary hypertension. Most commonly, it results from inappropriate ACTH secretion, being rarely caused by bilateral adrenocortical diseases, which include primary pigmented adrenocortical disease (PPNAD) or "micronodular adrenal disease," often associated with the Carney complex, and massive macronodular adrenocortical disease (MMAD), which is isolated in the majority of cases *(15)*. However, it has to be taken into consideration that though the most common hypercortisolism states are those secondary to an overt Cushing syndrome, subclinical forms deserve attention. The diagnosis of glucocorticoid resistance syndrome must also be considered. This is a rare disease characterized by a low sensitivity of the glucocorticoid receptor (GR), triggering increased ACTH levels that secondarily increase free cortisol production *(16)*. Molecular alterations associated to glucocorticoid resistance correspond to mutations of the GR gene *(17–19)*, and might be associated to metabolic syndromes like glucocorticoid resistance, glucocorticoid sensitivity, obesity, and essential hypertension. Moreover, a subtle elevation of urinary cortisol excretion has been described in approx 30% of 364 hypertensives defined as essential in a recent study performed by our group *(20)*; in them, the association with low renin and aldosterone levels suggests a mineralocorticoid action of F. Patient 2, in whom age, macroscopic findings, and the lack of a positive family history support the diagnosis of an isolated MMAD, expressed this mineralocorticoid activity of cortisol by a low serum potassium and a suppressed PRA even under converting enzyme inhibitors.

Diagnostic Evaluation and Management

Urinary fractionated catecholamines with an increase of norepinephrine excretion, with normal adrenaline or total catecholamines, could be helpful in diagnosing adrenal medullary hyperplasia *(8)*. In patient 1, elevated urinary normetanephrine follows this rule in spite of the predomi-

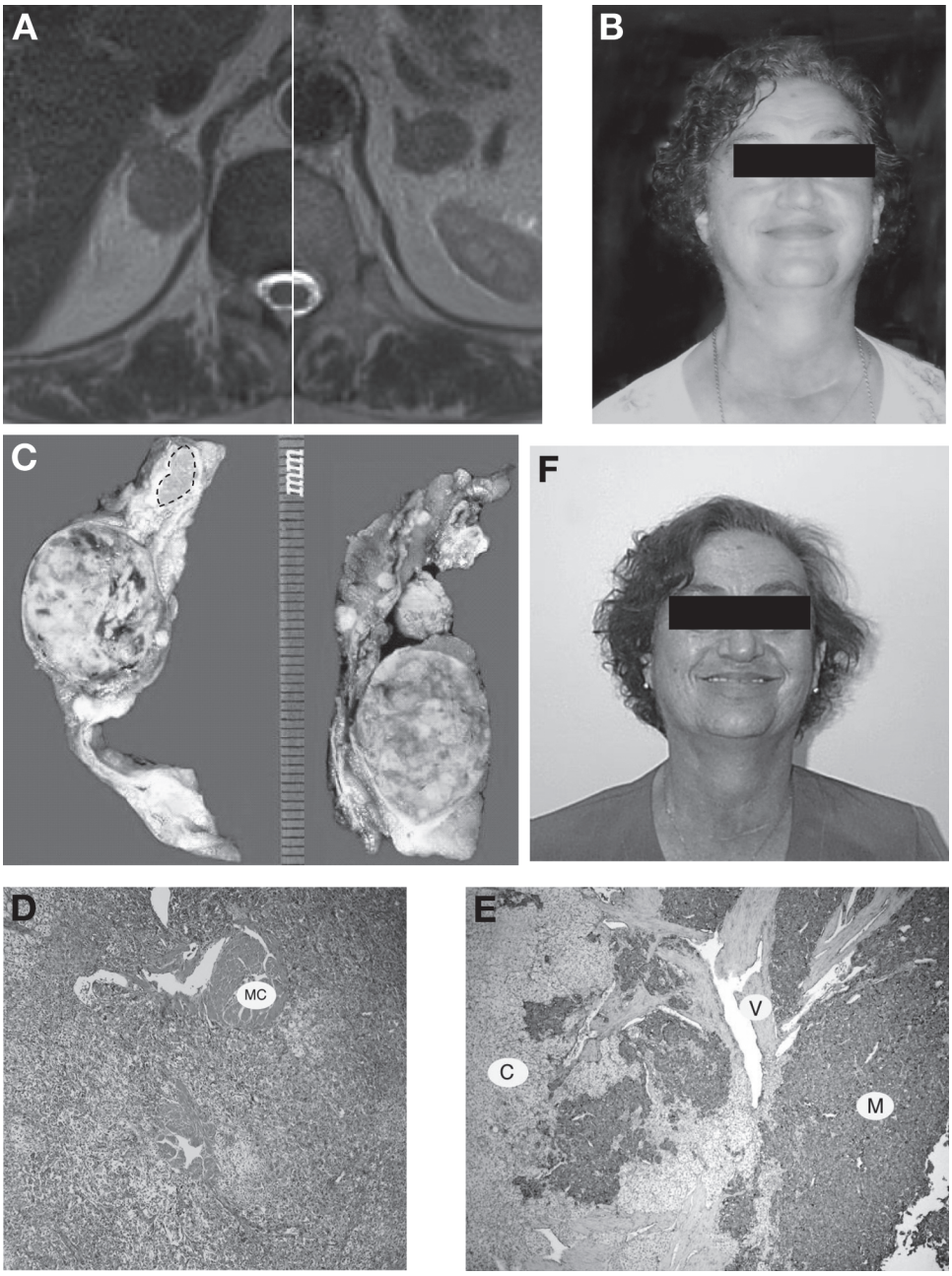

Fig. 2. (**A**) Sections of abdominal MRI showing bilateral adrenal nodes. (**B**) Mild plethora of face and neck. (**C**) Adrenal cortex with multiple cortical nodes and a thick adrenal medulla limited by the discontinuous line. (**D**) Microscopic exam of left adrenal gland showing cortical multinodular hyperplasia including areas of medullary cells (MC) (HE, ×100). (**E**) Chromogranin staining shows a thick medulla (M) and chromogranin positive cells in isolation, streamers and clusters included in the non-nodular cortical (C) zone (×100). V = vein. (**F**) Absence of facial plethora a month after adrenalectomy.

Table 2
Dexamethasone Suppression Tests Performed in Patient 2

	Urinary free cortisol (µg/24 h)	Serum cortisol (µg/dL)	Plasma ACTH (pg/mL)
Basal	352	17.6	<5.0
Dexamethasone 2 mg daily for 48 h	246	17.7	
Dexamethasone 8 mg daily for 48 h	205	16.7	

nance of epinephrine granules in the electron microscopy study, as may be expected from the presence of medullary phenylethanolamine-*N*-methyltransferase, which converts norepinephrine to epinephrine. The discordance between the predominant cellular granules and the urinary metanephrine may be explained by the stimulation of the autonomic adrenergic system by epinephrine, as has been shown for epinephrine infusions *(21)*.

A bilateral uptake of ^{131}I MIBG has been reported in 16–28% of normal adrenals, but a unilateral uptake is more sug-

Table 3
Upper Reference Ranges for Urinary Metanephrines[a]

		Upper limit for normotensive individuals	Diagnostic cut-off values for pheochromocytomas
Metanephrine (μg/24 h)	Females	180	400
	Males	261	
Normetanephrine (μg/24 h)	Third decade	390	900
	Eight decade	560	

Source: Mayo Medical Labs and Quest Diagnostic/Nichols Institute.
[a]In the normotensive population and in pheochromocytoma, separated by a grey zone that could include medullary hyperplasia.

Table 4
Clinical Pathological Features that Differentiate Pheochromocytoma from Adrenal Medullary Hyperplasia *(12,13,23)*

Pathological alterations	Pheochromocytoma	Adrenal medullary hyperplasia
Necrosis	Yes	No
Increased adrenal mass	No	Yes
Nodes	Yes	Yes
Medulla in both extremes adrenal gland	No	Yes
Ratio cortex:non-nodular medulla lower 10:1	No	Yes
Alveolar pattern	Yes	No
Cellular characteristics	Main adrenal cells	Giant cells
Cellular pleomorphism	Very frequent	Infrequent
Chromaphin granules	Diffuse	Variable

gestive of medullar hyperplasia *(22)*. However, bilaterally positive adrenals could reflect bilateral medullar hyperplasia, negative to tomography and resonance. When an adrenal medullar hyperplasia is suspected, be it sporadic or within the context of a MEN2 patient or kindred, but radioisotope imaging is negative, the patient may be treated with tailored α and β blockade, which, as preoperatively in patient 1, can achieve adequate blood pressure control. This option, recommended by Manger and Gifford *(23)*, may be also considered in subjects with persistent hyperadrenergia due to contralateral medullary hyperplasia. The postoperative fall in blood pressure and urinary metanephrines in our patient, added to the uptake of ^{131}I MIBG by the left adrenal gland, makes unilateral adrenal hyperplasia likely, as supported by the long-term follow-up in patients with unilateral adrenal resections *(24)*. The asynchronic pattern of adrenal medullary lesions and their potential progression, make a close clinical and biochemical follow up mandatory both in patients subjected to surgery or to medical treatment. Finally, the differential histological diagnosis between a pheochromocytoma and medullar hyperplasia is summarized in Table 4 *(12,13,23)*.

The diagnosis of Cushing syndrome is usually suspected by the classical clinical features. However, the autonomous glucocorticoid production without specific signs and symptoms of Cushing's syndrome, also known as subclinical Cushing syndrome, is considered as a much more frequent entity *(25,26)*. As in patient 2, it could present with progressive weight gain, with slight facial changes, and with increased fatigability, changes which in hypertensive women may be mistaken as postmenopausal complaints, precluding further studies. In both clinical and subclinical Cushing syndrome, the diagnostic approach is based in the lack of suppressibility of cortisol with dexamethasone (low and high doses) and the ACTH measurements.

After the biochemical diagnosis of Cushing's syndrome, CT scan or MR images of the adrenal glands must be obtained. Visualization of the adrenal mass by means of ^{131}I-norcholesterol scintigraphy has been advocated by several groups to screen for subclinical Cushing's syndrome, based on the observation that significant glucocorticoid production by the tumor will lead to unilateral tracer uptake, whereas the contralateral atrophic adrenal will be scintigraphically silent *(25)*.

As a general rule, hormonally active incidentalomas are surgically removed to prevent serious morbidity. However, it is still uncertain whether patients with subclinical Cushing's syndrome benefit from surgery, because the progression from subclinical disease to overt Cushing's syndrome occurs in a minority of cases. Surgery should be considered

whenever there is: (1) imminent progression to overt Cushing, (2) young age (<50 yr), (3) metabolic disease of recent onset possibly related to Cushing's syndrome (hypertension, obesity, diabetes) and (4) osteoporosis or osteopenia *(25)*.

Morpho-Functional Interactions Between Adrenal Cortex and Medulla

The histological association of adrenal medullar hyperplasia with either functioning or non-functioning adenomas originating from the reticulata or glomerulosa, as presented by our patients, has been communicated in a few reports *(27–31)*.

Routine histological studies describe a clear cut limit between the adrenal cortex and the medulla, zones conventionally considered as independent endocrine organs. However, specific staining for chromaffin or cortical cells reveals an intimate contact of chromaffin and cortical cells within the human adrenal *(6,32)*, provided by an irregular border devoid of fibrous tissue between the reticularis and medulla, a high degree of intermingling of the two endocrine cell types, and the presence of cortical cells in the medulla or vice versa, as can be appreciated in the biopsies of both our patients. Not only are these cell types in close apposition, but cortical cells extend filopodia toward chromaffin cells, while chromaffin granules line the cell membrane, probably preparing for exocytosis. In addition, the presence of gap junctions in the transition zone support an intraadrenal crosstalk *(33,34)*.

From a functional point of view, in addition to catecholamines, peptides produced by the adrenal medulla such as acetylcholine, serotonin, atrial natriuretic peptide (ANP), vasopressin, vasoactive intestinal peptide (VIP), galanin, and neuropeptide galanin, and pituitary adenylate cyclase-activating polypeptide (PACAP), stimulate steroid production *(6)*. On the other hand, steroids influence the enzymatic activity of phenylethanolamine-*N*-methyltransferase, which converts norepinephrine to epinephrine, and states of low corticoid synthesis such as congenital hyperplasia and Addison's disease are associated to decreased catecholamine secretion. In vitro studies have demonstrated that chromaffin cells co-cultured with cortical cells extend process toward or onto them, while their depolarization increases corticosterone secretion *(35)*.

The scarcity of the morphological association of cortical and medullary lesions, in spite of these functional interactions, is probably due to pathology exams addressed at the clinical syndrome and at the main macroscopic lesions. This approach disregards abnormalities in the supposedly normal gland, thus ignoring a clinical and pathological entity.

Conclusion

The description of these two cases should increase clinical awareness of subtle forms of adrenal hypertension presenting as sporadic cases or within familial syndromes. This is especially relevant as we are faced with malignant or potentially malignant diseases that require early diagnosis. An increased suspicion of adrenal medullar or cortical functional and anatomical alterations should raise the prevalence of adrenal hypertension both in its classical forms of pheochromocytoma and Cushing syndrome, as in the more elusive variants. From the pathologist's point of view, the awareness of the subtle clinical forms, and of the potent interaction between the medulla and cortex, should prompt a thorough dissection and microscopic observation of the adrenal gland, as well as the routine use of specific cell type markers.

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