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Cyclic Cushing syndrome and endocrine disorders in two children with Carney complex

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ABSTRACT

Carney complex (CC) is characterized by myxomas, pigmented skin lesions, and endocrine hyperactivity, with a predisposition to tumors. Primary pigmented nodular adrenocortical disease (PPNAD) is notable, manifesting with subclinical, progressive, or cyclical symptoms of Cushing's syndrome (CS) caused by endogenous adrenocorticotropic hormone-independent hypercortisolism, and characterized by a paradoxical increase in urinary free cortisol after a corticosteroid suppression test.

PPNAD should be suspected in patients with cyclic CS, and its association with CC should be considered. In cases of strong clinical suspicion, a suppression test should be performed to demonstrate the characteristic paradoxical response and ensure an early diagnosis to avoid the long-term repercussions of hypercortisolism.

We describe two patients with clinical and molecular diagnosis of CC who presented with PPNAD with a characteristic biochemical pattern treated with bilateral adrenalectomy in both cases.

Keywords: *Carney complex; Cushing syndrome.*

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INTRODUCTION

Carney's complex (CC) is characterized by the triad of myxomas, pigmented skin lesions, and endocrine hyperactivity, with a predisposition to tumors. It follows an autosomal dominant pattern of inheritance, with 70% of cases occurring within families.[1] Inactivating variants in the *PRKAR1A* gene are identified in 70-80% of cases.[1,2]

Diagnosis is based on clinical criteria; molecular testing is a complementary criterion (*Table 1*). Among its endocrinological manifestations, primary pigmented nodular adrenocortical disease (PPNAD) stands out, present in 25% of patients, which manifests with subclinical, progressive, or cyclical symptoms of Cushing's syndrome (CS) due to adrenocorticotropin hormon (ACTH)-independent hypercortisolism.[3] This condition is characterized by a paradoxical increase in urinary free cortisol (UFC) of more than 50% after a corticosteroid suppression test,[4] a phenomenon that would be caused by an increase in the expression of glucocorticoid receptors[4] or an aberrant coupling in the intracellular protein kinase A (PKA)-dependent pathway.[5] Other manifestations include asymptomatic elevations of growth hormone (GH), insulin-like growth factor 1 (IGF1), or prolactin; pituitary adenomas, large-cell calcifying Sertoli cell tumors (LCCST), among others.

Our aim is to describe two cases with clinical and molecular diagnosis of CC who presented PPNAD; to analyze the clinical and biochemical characteristics and the treatments instituted; and to identify associated endocrine disorders.

CLINICAL CASE 1

A 5-year-old boy was referred by the Dermatology Service for suspected CC. He was born at term and presented with cutaneous and subcutaneous myxomas resected at age 2 years. He had a maternal aunt with cardiac and cutaneous myxomas, ovarian and uterine cancer, and suspected CC.

He was eutrophic, with normal weight and height, prepubertal, with hyperpigmented macules on the face and lips compatible with lentiginosis, preauricular and thoracic myxomas, and scars from previous resections. He had an echocardiogram, testicular and thyroid ultrasound without abnormalities, and laboratory tests with normal thyroid profile, cortisol, and prolactin, with no clinical signs of endocrine involvement.

He was evaluated by Genetics, which requested a panel of genes associated with hereditary tumors, identifying a heterozygous variant classified as probably pathogenic in the *PRKAR1A* gene, NM_002734.5:c.781A>T;p.(Lys261Ter). Follow-up was recommended according to established guidelines.[2,5]

Nine months later, he consulted for increased appetite and weight gain, accompanied by hyperactivity. He maintained normal growth velocity and body mass index (BMI). Blood pressure (BP) was 108/66 mmHg (PC 90:110/70). He showed a rounded and flushed face, supraclavicular space occupation, increased

Table 1. Diagnostic criteria for Carney complex. Based on Stratakis[3]

MAJOR CRITERIA	• Cutaneous lentiginosis on the lips, conjunctiva, and mucous membranes. • Cutaneous-mucosal or cardiac myxomas. • Primary pigmented micronodular adrenocortical hyperplasia or paradoxical increase in UFC after dexamethasone. • Acromegaly associated with a GH-producing pituitary adenoma. • Testicular large-cell calcifying Sertoli cell tumor or calcifications on testicular ultrasound. • Thyroid carcinoma or multiple prepubertal hypoechoic nodules. • Psammomatous melanocytic schwannomas. • Blue nevi. • Mammary myxomatosis. • Multiple ductal mammary adenomas. • Osteochondromyxoma.
ADDITIONAL CRITERIA	• Affected first-degree relative. • Inactivating mutations in the *PRKAR1A* gene. • Activating mutations in the *PRKACA* or *PRKACB* gene.

UFC: urinary free cortisol; GH: growth hormone.
Carney complex is defined by two major criteria, one major criterion + one family member affected, or one major criterion + a confirmed variant.

abdominal fat, and dorsal hair growth.

With suspected CS, initial hormone studies were normal, however a 1 mg dexamethasone suppression test showed no cortisol suppression, and a 2 mg dexamethasone test showed a paradoxical increase in cortisol (46%), confirming endogenous hypercortisolism *(Table 2).*

Given the association between CC and PPNAD, an abdominal computed tomography (CT) scan with thin slices was requested, showing no lesions *(Figure 1A).*

Over time, the patient had reduced appetite and weight loss, with less facial flushing, confirming cyclical CS.

We decided to perform bilateral adrenalectomy guided by indocyanine green contrast. Histopathological analysis confirmed PPNAD in both adrenal glands (*Figure 1B*). The patient recovered favorably; supplementation with hydrocortisone and fludrocortisone was initiated.

During follow-up, bilateral testicular calcifications associated with a nodular lesion in the left testicle were detected (*Figure 1C*), with normal prepubertal levels of antimüllerian hormone (AMH) and testosterone. Due to the nodule growth, a biopsy was performed, confirming LCCSCT (*Figure 1D*). He presented with transient and asymptomatic elevation in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels.

The patient continues under regular clinical and ultrasonographic monitoring.

CLINICAL CASE 2

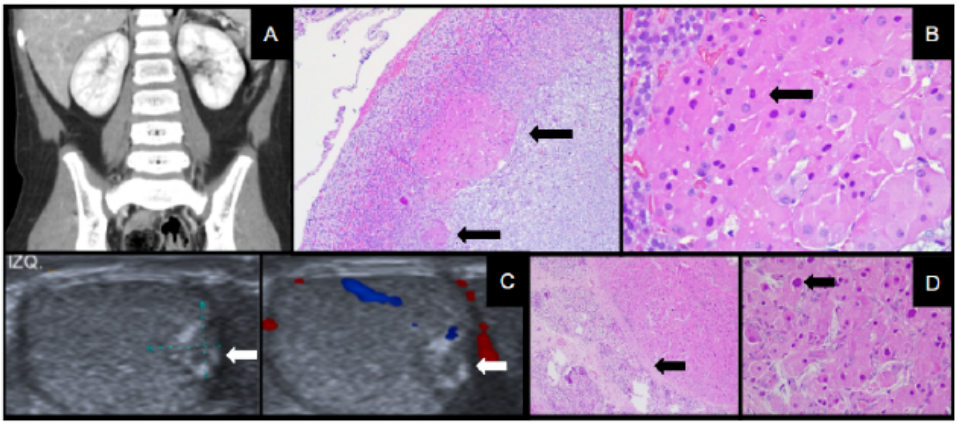
A 7-year-old boy, previously healthy, presented spontaneously to the Endocrinology Department with obesity and weight gain. He reported that, one year prior to presentation, he

Table 2. Hormonal studies at the onset of clinical symptoms

	CASE 1	Reference	CASE	Reference
Adrenal axis				
ACTH (pg/ml)	11.3	5-46	7.5	5-46
Basal cortisol (µg/dl)	16.1	3.9-24	4.9	5-30
Cortisol in suppression test - dexamethasone 1 mg (µg/dl)	**8.3**	<1.8	**9.3**	<1.8
Cortisol in suppression test - dexamethasone 2 mg (µg/dl)	**11.9**	<1.8	**21.3**	<1.8
Cortisol in suppression test - dexamethasone 8 mg (µg/dl)	-	-	**31.1**	<1.8
Nocturnal salivary cortisol (µg/dl)	0.14	0.14	**0.39**	<0.14
Dehydroepiandrosterone sulfate (ng/ml)	<150	80-870	<150	73-991
Delta 4 androstenedione (ng/ml)	<0.4	0.05-0.45	<0.3	0.05-0.45
17OH progesterone (ng/ml)	0.54	0.33-1.2	0.54	0.33-1.2
Basal UFC 1 (µg/m^2)	64	<72	8.8	<72
Baseline UFC 2 (µg/m^2)	70.4	<72	32.8	<72
UFC after 2 mg supression test (µg/m^2)	**118**	<72	**282**	<72
UFC after 8 mg supression test (µg/m^2)	-	-	**418**	<72
Somatotropic axis				
GH (ng/ml)	3.1	0.09-2.5	**6.7**	0.16-5.4
IGF-1 (ng/ml. SD)	**209 (+1.9)**	22-208	**315 (+2.3)**	57-277
BP3 (mg/L)	-	-	**6.3 (+2.3)**	2.6-4.8
Thyrotropic axis				
TSH (mIU/ml)	1.26	0.82-4.74	1.68	0.92-4.38
T4 (ug/dl)	8.9	6.1-10.9	9.7	6-16.4
Free T4 (ng/dl)	1.1	0.91-1.91	1.08	1.01-2.08
T3 (ng/ml)	1.1	0.99-2.14	2.74	0.93-2.3
Gonadal axis				
LH (mIU/ml)	0.06	<0.3	0.2	<0.3
FSH (mIU/ml)	0.14	<0.3	2.3	<0.3
Testosterone (ng/ml)	0.09	<0.36	0.06	<0.28
AMH (pmol/l)	726	238-1108	299	96-1131
Estradiol (pg/ml)	<13	<13-19	<13	<13-19

ACTH: adrenocorticotropic hormone; UFC: urinary free cortisol; GH: growth hormone; IGF-1: insulin-like growth factor 1; BP3: binding protein 3; SD: standard deviation; TSH: thyrotropin; T3: triiodothyronine; T4: thyroxine; LH: luteinizing hormone; FSH: follicle-stimulating hormone; AMH: antimüllerian hormone.

Figura 1. Additional studies for case 1



A: Abdominal Computer Tomography: No abnormalities.
B: Histologic sections of bilateral adrenalectomy: On the left, a microscopic nodular lesion (arrow), well defined, without capsule, immersed in the adrenal cortex. A smaller lesion with similar characteristics is evident nearby (arrow). On the right, a larger magnification of the lesion shows the large, eosinophilic cytoplasm of the nodule cells (arrow), which contrasts with the normal cells of the adjacent adrenal cortex.
C: Testicular ultrasound: A nodular image (arrow) measuring 5 × 4.5 mm with peripheral calcifications and poor vascularization is evident.
D: Histologic sections of testicular lesion: On the left, proliferation of large cells with extensive eosinophilic cytoplasm and an irregular capsule (arrow) containing them and separating them from the adjacent healthy testicular parenchyma. On the right, greater magnification shows some large, hyperchromatic nuclei (arrow), with no calcifications in the material studied.

had experienced weight gain, facial rounding, and facial flushing lasting three months, followed by a 9-month asymptomatic period, suggesting a diagnosis of cyclical Cushing syndrome (CS).

His height was between the 25 and 50 percentiles, he had central obesity (weight Z score 2.3), Cushingoid facies, Tanner stage G1 PH2, 2 ml testicles, hirsutism, and BP at the upper limit (109/69 mmHg, 95 BP percentile for height: 111/72).

Hormonal studies showed elevated nocturnal salivary cortisol, a 1 mg dexamethasone suppression test with no cortisol suppression, and a 2 mg dexamethasone suppression test with a paradoxical increase in UFC (859%), confirming endogenous hypercortisolism (*Table 2*).

Abdominal ultrasound and CT scans showed both adrenal glands visible, heterogeneous, and enlarged (*Figure 2B*).

With a strong suspicion of PPNAD, further tests were requested to assess whether he met the criteria for CC. Results were normal, except for elevated baseline GH and IGF1 levels. An oral glucose tolerance test showed lack of GH suppression, indicating autonomous secretion, and a brain MRI identified a 2 mm lesion compatible with a pituitary microadenoma.

The results were interpreted as CC, and confirmed by the identification of a deletion involving part of the *PRKAR1A* gene NM_002734.5:c.348+314_709-699del, classified as likely pathogenic.

Bilateral adrenalectomy was indicated, and PPNAD was confirmed in both adrenal glands (*Figures 2C* and *2D*). The patient progressed favorably and was supplemented with hydrocortisone and fludrocortisone.

On reassessment of the somatotropic axis after surgery, GH and IGF1 values were normal, so a watchful waiting approach was maintained. During follow-up, bilateral testicular microcalcifications without associated nodules were detected. The patient remains under periodic clinical and ultrasound monitoring with good overall progress.

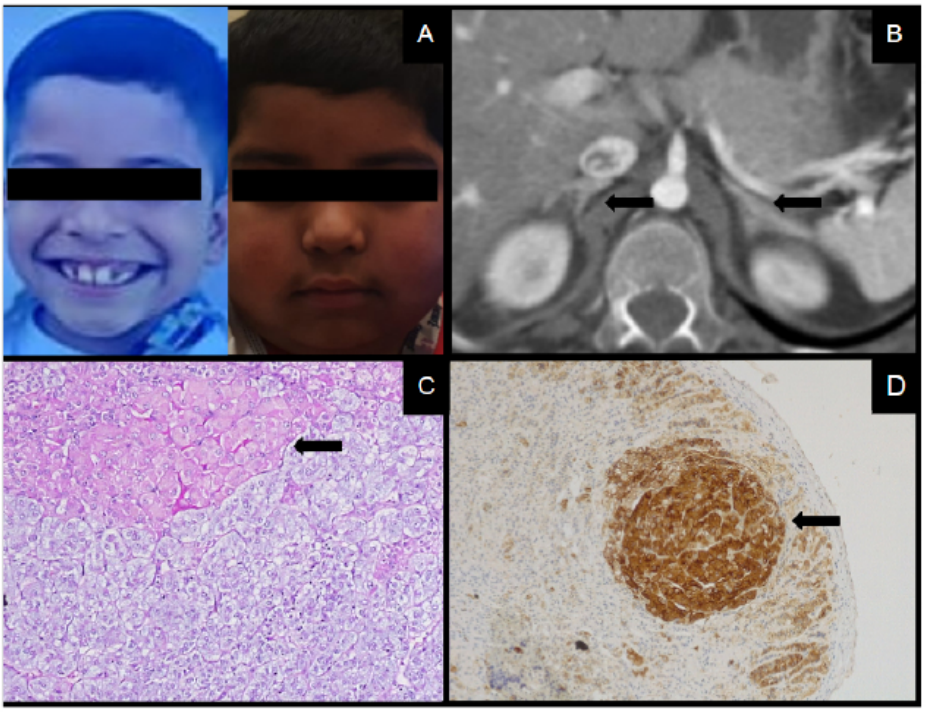
DISCUSSION

We describe two patients with CC, a rare syndrome that was confirmed by molecular testing.

Both cases illustrate classic manifestations such as cyclic CS associated with PPNAD, a severe and potentially life-threatening clinical condition. In the first case, the diagnosis was made promptly, as the patient was being monitored for CC; however, in the second case, CS was not initially suspected.

In hypercortisolism, growth retardation is a sign that accompanies obesity and distinguishes it from simple obesity. However, in PPNAD, concomitant androgen hypersecretion, combined

Figure 2. Images and complementary studies of case 2



A: Photographs of the patient: Left, one year before diagnosis, and right, at the first consultation at the service.
B: Computed axial tomography of the abdomen with contrast showing enlargement of both adrenal glands (arrows), the right one measuring 3.5 mm and the left one 7.98 mm in anteroposterior diameter, with slight heterogeneity in contrast enhancement.
C: Pathological anatomy of bilateral adrenalectomy: Several well-circumscribed nodular foci (arrow) are observed, unencapsulated and less than 1 mm in size at the cortical level, consisting of large cells with eosinophilic cytoplasm and vesicular nuclei, and isolated cells show a light brown granular pigment.
D: Pathological anatomy of bilateral adrenalectomy: Synaptophysin-positive immunohistochemistry is observed (arrow).

with the cyclical nature of hypercortisolism, can mitigate this clinical sign.

In case 1, molecular testing confirmed the diagnosis of CC, provided warning signs, and allowed close monitoring, leading to early diagnosis after a single cycle compatible with CS. In case 2, the first cycle was not recognized, delaying diagnosis until the second cycle.

Endogenous CS is diagnosed by detecting elevated UFC, loss of circadian rhythm with elevated nocturnal salivary cortisol (as seen in case 2), and lack of supression in tests (in both patients). However, the biochemical hallmark of PPNAD is a paradoxical increase in UFC during the dexamethasone suppression test.

Bilateral adrenalectomy in one stage is the first-line treatment,[2] even if the characteristic "pearl necklace" images generated by the presence of nodules smaller than 1 cm surrounded by atrophic areas[6,7] (only visible in case 2) are not observed.

Regarding associated endocrine disorders, both patients presented with altered somatotropic axis. Elevations in GH, IGF-1, or abnormal GH suppression in oral glucose tolerance testing have been reported in up to 75% of cases, with 10–12% of pituitary adenomas. These findings are usually transient and asymptomatic, so the recommended approach is observation.[8]

LCCSCT represent about 1% of testicular tumors and are characterized by AMH production and aromatase activity with increased estradiol levels (which can lead to gynecomastia), though they are not always clinically evident, as seen in both of our patients. Current guidelines classify LCCSCTs as benign, and the recommended management is expectant,[9] unless compressive symptoms or signs of malignancy are present. In case 1, the increase in size and the presence of an associated nodule led to a biopsy, and malignant transformation was ruled out.

Long-term surveillance is essential in patients with CC, particularly given the risk

of complications such as testicular tumors or additional endocrine disorders. These cases reinforce the need for a personalized approach and ongoing follow-up in patients with CC, contributing to a better understanding of this rare entity and its phenotypic variability.

PPNAD should be suspected in patients with cyclic Cushing syndrome, and its association with CC should be considered. In cases of strong clinical suspicion, a suppression test should be performed to demonstrate the characteristic paradoxical response and allow an early diagnosis to avoid the long-term repercussions of hypercortisolism. ■

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