Cushing's Syndrome Revealing Carney Complex: A Case Report

Abstract

Carney complex (CNC) is a rare multisystem disorder, inherited in an autosomal dominant manner and characterized by distinctive spotty skin pigmentation, myxomas and endocrine abnormalities. We report a case of a 35-year-old patient diagnosed with Cushing's syndrome complicated with an impaired glucose tolerance (IGT) and a severe psychiatric disturbance. The diagnosis of CNC was made by having two major criteria, namely a primary pigmented nodular adrenal disease (PPNAD) and thyroid carcinoma.

Keywords: Primary pigmented nodular adrenal disease; Cushing's syndrome; Carney complex; adrenalectomy; Thyroid carcinoma

Case Report

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Abbreviations: CNC: Carney Complex; IGT: Impaired Glucose Tolerance; PPNAD: Primary Pigmented Nodular Adrenal Disease; ACTH: Adrenocorticotropic Hormone; LCCSCT: Large Cell Calcifying Sertoli Cell Tumors

Introduction

Carney Complex (CNC) is a rare syndrome, first described by JA Carney et al. [1]. It is inherited in an autosomal dominant pattern in 70% of cases with a variable expressivity and almost complete penetrance up to 70-80% by the age of 40 or occurring less commonly sporadically as a result of a de novo mutation [2,3]. Previously, it was called NAME (nevi, atrial myxoma, ephelides) and LAMB (lentigines, atrial myxoma, blue nevi) syndrome [4,5].

CNC is characterized by the presence of cardiac and muco-cutaneous myxomas, pigmented skin lesions, multiple endocrine and nonendocrine tumors.

Endocrine manifestations include primary pigmented nodular adrenal disease (PPNAD), pituitary tumors, large cell calcifying Sertoli cell tumors of the testicles and thyroid neoplasms [6].

In this article, we describe the management and the follow-up of a female patient with Cushing's disease and the diagnostic criteria to retain the diagnosis of CNC.

Case Report

A 35-year-old female was referred in Mai 1999 to our department for oligomenorrhea, baldness and weight gain evolving over 2 years. She doesn't have any medical record and she is not taking any specific treatment especially corticosteroids. In her familial history, we found a sister and a niece with breast cancer and a brother died of colon cancer. The physical exam revealed a moon face, a moderated hirsutism, a buffalo neck, an abdominal obesity, a red striae and a thin skin (Figure 1).

The blood pressure was normal and the biochemical finding confirmed an impaired glucose tolerance (IGT) with an altered serum cortisol circadian rhythm (Table 1). A low dose dexamethasone suppression test returned negative confirming the Cushing's disease (Table 1). ACTH level was low (Table 1) and an abdominal CT-scan revealed a bilateral adrenal hyperplasia with two nodules measuring 2 cm in each gland.

During her second admission in September 1996, the patient presented a severe depression with anxiety, hallucination, a suicide attempt. She took antidepressant medication associated with neuroleptics with several side effects. The patient received also aminoglutethimide 125 mg b.i.d associated with hydrocortisone for 37 days. A multidisciplinary staff recommended the surgery after the stabilization of her psychiatric affection. She underwent a bilateral adrenalectomy after a medical preparation in November 10, 1999 without incidence. The histopathologic finding revealed a nodular hyperplasia of the adrenal cortex and the presence of a brown pigmentation colored like lipofuscin recalling the possibility of CNC.

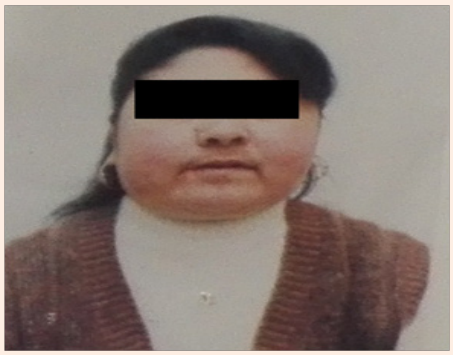

Figure 1: The patient presented with Cushing signs (1999).

We looked for other features of CNC and specialized exams were made. The dermatologic exam found a naevocellular naevi in the face in addition to a histiocytofibroma of the thigh and a molluscum pendulum. No blue nevus nor periorificial lentigines were found. Echocardiography was negative for cardiac myxomas. abdominal and pelvic ultrasound found only a small corporeal uterine myoma. Echo mammography found bilateral cystic formations without atypia.

Table 1: Biochemical parameters before and after the bilateral adrenalectomy.

	May 1999	October 1999	2001	2003	2004	2005	2007	2009
Fasting Plasma Glucose (g/l)	0,9		0,72	0,7				0,75
Two-hour Postprandial Glucose (g/l)	1,44		0,86					
8 A.M.-Serum Cortisol (ng/l)	209							
4 P.M.-Serum cortisol (ng/l)	273							
Low-dose Dexamethasone Suppression Test (ng/l)	217							
ACTH (ng/l)		6,5		6,19	295,7	340	17,9	
Testosterone (ng/ml)		1,6						
Estradiol (pg/ml)		12,7					315	
Prolactin (ng/ml)		6					11,9	
FSH (mIU/l)		7					3,2	
LH (mIU/l)		1,2					5,1	
TSH (mIU/l)		1,19					3,7	2,4
FT4 (pmol/l)		15,9					15,6	13,1

During the first two years following the surgery, she stopped several times her psychiatric consultation, she took her medications irregularly and was admitted once for acute adrenal insufficiency after stopping her replacement therapy with 30 mg q.d of hydrocortisone and 50 µg q.d of fludrocortisone.

She has been on regular follow-up afterwards with a clinical regression of the signs of hypercorticism, a disappearance of the IGT and a lot of improvements in the depression symptoms (Figure 2). From 2004, the patient reported headaches and a visual impairment.

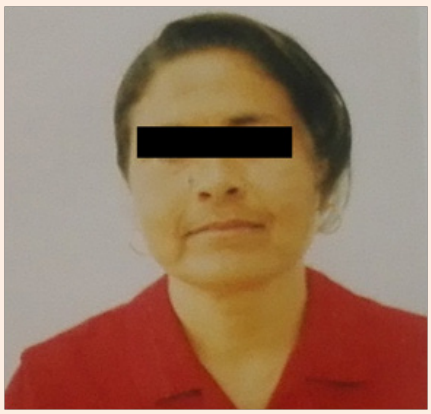

Figure 2: Regression of Cushing signs (2004).

Considering the elevation of ACTH level (Table 1), a pituitary MRI was performed eliminating a Nelson's syndrome.

In 2009, a nodular goiter was revealed in the physical exam and the cervical ultrasound was performed showing a suspicious left nodule measuring 27 x 15 mm, heterogenous, having a double vascularization and a microcalcifications. The thyroid hormone, antibodies (TPO = 5 IU/ml, TG = negative) and calcitonin (< 2 ng/l) was in the normal range. The patient underwent a total thyroidectomy in October 2009 revealing a papillary microcarcinoma in addition to two benign vesicular adenomas in the final histopathological examination. The patient received two 100 mCi radioactive Iodine cure with a complete remission.

Discussion

CNC is a rare autosomal dominant genetic disorder affecting more than 750 patients distributed in many ethnic groups and equally between males and females [6,7]. 70% of patients are found to have inactivating mutations in the protein kinase A type I-alpha regulatory subunit (PRKAR1A) gene on chromosome 17q22-24 [8,9]. Other genes identified as causing CNC are PDE11A and PDE8B [9].

The diagnosis of CNC is difficult given the variable clinical manifestations and the different possible combinations of signs (Table 2). Therefore, diagnostic criteria have been established and a patient is considering having this syndrome if he has either two of the major criteria or one major and one supplemental criteria (Table 3).

PPNAD is a common manifestation affecting 25-60% of CNC patients and concerning mostly females (Table 2). Its causes an ACTH-independent Cushing's syndrome with specific characteristics (Table 4).

Our patient presented initially with a typic Cushing's symptoms complicated with ITG and essentially severe psychiatric manifestations. A high serum cortisol value after low-dose dexamethasone suppression test has been objectified associated with a low ACTH level. An abdominal CT-scan confirmed a bilateral adrenal hyperplasia with a bilateral macronodule. Despite, this aspect wasn't the typical one in CNC patients but it could be found up to 20-30% (Table 4).

The decision of the surgery was made, after a multidisciplinary staff and an informed consent from the patient, revealing a pigment stained like lipofuscin which was also described in PPNAD (Table 4). In CNC patients, the best treatment for PPNAD is a bilateral adrenalectomy. A medical treatment with steroidogenesis inhibitors may also be considered (Table 5).

The follow-up of the patient has revealed a suspicious thyroid nodule that was confirmed later to be a papillary microcarcinoma. Papillary or follicular thyroid carcinomas are considered as a major criterion of CNC (Table 3) and can be found up to 10% (Table 2). The CNC patients need a continuous surveillance at least yearly in order to detect early the manifestations of this syndrome (Table 6). The cardiac diseases are responsible for more than half of the mortality risk in CNC patients dominated by the complications of heart myxomas and followed by the metastatic tumors (25%) [7].

Table 2: CNC manifestations [6,10-12].

Manifestations	Percentage
Cutaneous Manifestations	**80%**
Cutaneous Myxomas	30–55%
Multiple Blue Nevi	40%
Periorificial Lentigines	62%
Cardiac Manifestations	
Cardiac myxomas	20–40%
Pituitary Tumors	
Asymptomatic elevation of GH	75% (most cases without imaging evidence of pituitary adenoma)
Acromegaly	10-12%
Large Cell Calcifying Sertoli Cell Tumors (LCCSCT)	41-70%
Breast Tumor	14-25%
Ovarian Cysts	14%
Adrenocortical Tumors	
Primary Pigmented Nodular Adrenal Disease	25–60% (70-71% female and 21% males)
Thyroid Neoplasms	
Thyroid Nodules	60% (75% nonspecific cystic disease;
Thyroid Cancer (Papillary or Follicular)	25% follicular adenoma) 10 %
Psammomatous Melanotic Schwannomas	**10% (10% malignant degeneration risk)**
Pancreatic Neoplasms	**2.5%**

Table 3: Diagnostic criteria for CNC [6].

	Supplemental Criteria
1	Affected first-degree relative
2	Activating pathogenic variants of PRKACA (single base substitutions and copy number variation) and PRKACB
3	Inactivating mutation of the PRKAR1A gene

	Minor criteria (Findings Suggestive of or possibly Associated with CNC, but not Diagnostic for the Disease)
1	Intense freckling (without darkly pigmented spots or typical distribution)
2	Blue nevus, common type (if multiple)
3	Café-au-lait spots or other 'birthmarks'
4	Elevated IGF-I levels, abnormal glucose tolerance test, or paradoxical GH response to TRH testing in the absence of clinical acromegaly
5	Cardiomyopathy
6	History of Cushing's syndrome, acromegaly, or sudden death in extended family
7	Pilonidal sinus
8	Colonic polyps (usually in association with acromegaly)
9	Multiple skin tags or other skin lesions; lipomas
10	Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)
11	Single, benign thyroid nodule in a child younger than age 18 years; multiple thyroid nodules in an individual older than age 18 years (detected on ultrasound examination)
12	Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors

Table 4: Characteristics of Cushing's syndrome related to PPNAD [9,12,13].

Possible intermittent hypercortisolism initially
Misleading in childhood: may not slow growth rate (fluctuating hypercortisolism and possible association of GH hypersecretion)
ACTH-Independent Cushing's syndrome
Possible paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle's test
Both adrenals are affected
Adrenal CT-scan: Normal (30%) Unilateral or bilateral macronodule (1 to 3 cm, 20-30%) Micronodular hyperplasia
Bilateral hyperfixation of the adrenal at iodocholesterol scintigraphy (very rarely unilateral hyperfixation)
Histopathology: Normal weight of the adrenal glands Black, brown or red pigmented micronodules (lipofuscin was present within most of the enlarged cortical cells) Atrophy of the internodular cortex (usually)

Table 5: Treatment of CNC manifestations [2,3,6].

Cardiac Myxomas	Surgical removal (Risk of multiple heart Surgeries due to Recurrence of the Myxomas)
Cutaneous Myxoma	Surgical Excision
Cushing's Syndrome (Primary Pigmented Nodular Adrenal Disease)	Bilateral Adrenalectomy (possible Treatment by Steroidogenesis Inhibitors)
GH-Producing Pituitary Adenoma	Surgery or Somatostatin Analogues
Thyroid Tumors	Fine-needle Aspiration / Surgery if Malignancy is Suspected
Large cell Calcifying Sertoli cell Tumors	Surgery or aromatase inhibitors
Psammomatous Melanotic Schwannomas	Complete Surgical Resection if Possible
Osteochondromyxoma	Excision if Local Invasiveness

Table 6: Surveillance of CNC patients [2,3,6].

Regular skin evaluation
Monitoring of growth rate and annual pubertal staging in pre-pubertal children
Annual measurement of urinary free cortisol or an overnight 1-mg dexamethasone test
Annual measurement of plasma IGF-1, serum GH and prolactin beginning in adolescence
Annual echocardiography beginning in infancy (may be performed biannually if history of excised myxoma)
Clinical examination and annual thyroid ultrasound
Annual testicular ultrasound in males
Annual abdominal ultrasound of the ovaries in females
Clinical, ultrasonography or MRI follow-up of breast lesions in females

Conclusion

CNC is a rare disease and its variable manifestations can make the diagnosis much difficult. The association of determined criteria can easily lead to the diagnosis of this disease. The search of the genetic mutation can help finding the familial cases. An adequate treatment of each symptom is recommended to reduce the morbidity and the mortality related to this syndrome.

Conflict of Interest

None.

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