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Carney Complex: a familial lentiginosis predisposing to a variety of tumors

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Abstract

Carney complex is a familial lentiginosis syndrome; these disorders cover a wide phenotypic spectrum ranging from a benign inherited predisposition to develop cutaneous spots not associated with systemic disease to associations with several syndromes. Carney complex is caused by *PRKARIA* mutations and perturbations of the cyclic AMP-dependent protein kinase (PKA) signaling pathway. In addition to the cutaneous findings, the main tumors associated with Carney complex are endocrine: 1) primary pigmented nodular adrenocortical disease, a bilateral adrenal hyperplasia leading to Cushing syndrome; 2) growth-hormone secreting pituitary adenoma or pituitary somatotrophic hyperplasia leading to acromegaly; 3) thyroid and gonadal tumors, including a predisposition to thyroid cancer. Other tumors associated with Carney complex include: 1) myxomas of the heart, breast and other sites; 2) psammomatous melanotic schwannomas which can become malignant; 4) a predisposition to a variety of cancers.

Keywords

Carney complex; primary pigmented nodular adrenocortical disease; myxomas; schwannomas; acromegaly

Introduction

By 1981, a young man had been in and out the National Institutes of Health (NIH) Clinical Center for a variety of ailments; he had first been diagnosed with a growth-hormone producing tumor but his investigation and treatment was complicated by the baffling concurrent diagnosis of testicular tumors and hypercortisolemia due to adrenal tumors [1]. Before the end of the year, this patient was found dead at his home; "...this combination of lesions is best explained by the concept of neurocristopathies" is what the medical examiner in rural Pennsylvania concluded finishing his report on the autopsy of this 19-year-old

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Compliance with ethical standards

Conflict of interest

The author declares that he has no conflict of interest.

heavily freckled man who died in 1981 due to malignant, metastatic pigmented melanotic schwannoma. It was clear that he was affected simultaneously by two rare endocrine conditions, acromegaly and Cushing syndrome; several physicians had noted his many “freckles” and other pigmented skin lesions, but his disease was not actually diagnosed until years later. We finally diagnosed him with Carney complex (CNC) in 1995 (data not shown).

The association of myxomas, spotty skin pigmentation (lentigines) and endocrine overactivity was first reported by Dr. J. Aidan Carney in 1985 and subsequently designated as CNC in 1986 [2] and Carney syndrome by others [3] in 1994. With the report of this new syndrome it was realized that the majority of patients previously characterized under the separate diagnoses of LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) and NAME (nevi, atrial myxoma, myxoid neurofibroma, epheleide), would now be more appropriately described under CNC [2,3]. The diagnosis of CNC is made if two of the main manifestations of the syndrome are present (Table 1); these need to be confirmed by histology, biochemical testing or imaging; alternatively the diagnosis is made when one of the criteria is present and the patient is a carrier of a known inactivating mutation of the *PRKARIA* gene [5, 6] (Table 2).

Clinical manifestations

The most common features of CNC (Table 1) include spotty skin pigmentation (Figures 1 and 2) (lentigines, freckling, café-au-lait spots, and blue nevi), myxomas of the heart, skin (Figure 1G), and breast, and primary pigmented nodular adrenal cortical disease (PPNAD) associated with an atypical form of Cushing syndrome (CS) [6, 7]. The breadth of involved organs in CNC is quite unique; CNC is both a multiple endocrine neoplasia (MEN) (along with MEN-1 and -2) and a cardiocutaneous syndrome (such as Noonan syndrome and related conditions [8]. Of the non-cutaneous lesions found in CNC, cardiac myxomas are the most common [6]. These tumors tend to be of a more aggressive nature when compared to sporadic, non-CNC-associated myxomas: unlike the latter, the former may be in any cardiac chamber and may present multiple times, starting at a very young age (even in infancy) and without any predilection for gender (sporadic myxomas are more common in older women and almost always occur in the left atrium as single one-time tumors). Historically, cardiac myxomas have been reported to be responsible for more than 50% of the disease-specific mortality among CNC patients.

Endocrine gland involvement includes growth hormone (GH) secreting pituitary adenomas, thyroid gland disease, corticotropin (ACTH)-independent CS secondary to primary pigmented nodular adrenocortical disease (PPNAD), and testicular tumors, in particular, large cell calcifying Sertoli cell tumors (LCCSCT). Overall, PPNAD is the most common endocrine lesion and causes the greatest degree of endocrine-associated morbidity [7] (discussed in more detail below). In male patients, however, the occurrence of LCCSCT may supersede PPNAD in number, but not in morbidity, as it is typically a benign lesion most often diagnosed during routine testicular ultrasound when microcalcifications are found. Leydig cell tumors and adrenal rests have also been reported. Ovarian cysts are often found by sonographic examination as multiple hypoechoic lesions and although usually clinically insignificant they may progress, occasionally, to ovarian carcinoma [9, 10].

Thyroid gland disease spans the spectrum from nodular disease to carcinoma, but in contrast to pituitary and adrenal pathology, there does not appear to be an increased risk of hyper- or hypothyroidism [11]. By sonographic examination, more than 60% of children and adults with CNC will be found to have cystic or multinodular disease. On biopsy, follicular adenoma is the most common finding, whereas thyroid cancer, follicular or papillary, may develop in up to 10% of CNC patients with preexisting thyroid pathology [11]. Of note, recent examination for loss-of-heterozygosity (LOH) at the CNC locus on chromosome 17 (17q22-24) in sporadic thyroid cancer has found increased loss of this region, supporting the hypothesis that thyroid tissue is susceptible to tumorigenesis induced by *PRKARIA* loss of function [12].

Molecular genetics

Genetic linkage analysis has revealed two distinct loci for CNC, one on chromosome 2p16 (*CNC2*) and the other on chromosome 17q22-24 (*CNC1*) [13, 14]. Inactivating mutations of the gene encoding the protein kinase A type I- α regulatory (R1 α subunit (*PRKARIA*) were identified in all patients mapping to the chromosome 17 and analysis of families registered in the National Institutes of Health-Mayo Clinic collection has revealed that most CNC patients have mutations at the *CNC1* locus [13]. The gene responsible for CNC at the chromosome 2p16 locus is unknown. At this point, there are no clear phenotypic differences between families mapping to one or the other locus.

The role of R1 α in human tumorigenesis has been explored in several different cancer tissues and cell-lines. Enhanced expression of R1 α has been shown to play a role in colorectal, renal, breast, and ovarian cancer, and malignant osteoblasts, and may be associated with more advanced disease [15]. The notion of reduced R1 α activity had not been investigated prior to the discovery of it being the protein that was defective in CNC; CNC represents the first identified human disease associated with a mutation of the PKA heterotetramer [4]. The majority of mutations in the *PRKARIA* gene result in premature stop codons and predicted mutant protein products are not found in affected cells secondary to nonsense mRNA mediated decay (NMD) of the mutant sequence [14, 16].

Biochemically, loss of R1 α leads to increased cAMP-stimulated total (but not PKA-specific) kinase activity that is thought to be secondary to up-regulation of other components of the PKA tetramer, including both type I (*PRKAR1B*) and type II (*PRKAR2A* or *PRKAR2B*) subunits, in a tissue dependent manner [15]. Initial data supported the role of *PRKARIA* as a “classic” tumor-suppressor gene with tumors from CNC patients exhibiting germline mutations and subsequent LOH at the *PRKARIA* locus; however, it now appears that haploinsufficiency of *PRKARIA* may be sufficient for phenotypic expression of increased PKA activity [16] and the development of certain tumors, such as eyelid myxomas [17]. This concept is exemplified in animal models of CNC: whereas mice homozygous for R1 α deletions die early in utero [18], transgenic mice with heterogeneous expression of an antisense transgene for exon 2 of *PRKARIA* exhibit many of the phenotypic characteristics of CNC patients, including thyroid follicular hyperplasia and non-dexamethasone suppressible hypercortisolism [19, 20]. Not all of these lesions exhibited consistent losses of the normal R1 α allele. PKA is a ubiquitous serine-threonine kinase intimately involved in

the regulation of cell growth, including a potential role in chromosome stability [5]. The cross-talk between signal transduction pathways and the tissue specific effects of altered PKA function are inherently quite complex, reflected by at times conflicting data. For example, alterations of 17q and/or the *PRKARIA* locus have been found in both sporadic adrenal and thyroid cancers [12] yet allelic loss of 17q in cardiac and skin myxomas from CNC patients, with known germline *PRKARIA* mutations have not been found. Interestingly, CNC myxomas appear to have a more aggressive nature when compared to sporadic, non-CNC-associated myxomas, as discussed previously.

The physiologic impact of *PRKARIA* -inactivating mutations has been most thoroughly studied in PPNAD, a rare form of ACTH-independent CS, which is present in approximately one third of CNC patients. PPNAD often presents in an indolent fashion and may be difficult to diagnose due to an intermittent or cyclical nature of the associated hypercortisolism. Diagnosis is established using the six-day Liddle test as patients with PPNAD show a classic paradoxical rise in the 24 hour urinary free cortisol and/or 17-hydroxysteroids of more than 50% on the second day of high dose dexamethasone administration [6, 7]. Investigation of one of the signaling pathways, the mitogen-activated protein kinase (MAPK) ERK 1/2 pathway, typically inhibited by PKA in many cells, has recently been reported. In this report, the lymphocytes from CNC patients with known *PRKARIA* mutations showed altered PKA activity and increased ERK 1/2 phosphorylation. Cell metabolism and cell proliferation studies suggested that altered PKA activity is associated with reversal of PKA-mediated inhibition of the MAPK pathway resulting in increased cell proliferation [16].

Laboratory evaluation and genetic testing

The recommended clinical surveillance of patients with CNC differs per age group. For post-pubertal pediatric and adult patients we recommend annual echocardiogram (this study may be needed biannually for adolescent patients with a history of excised myxoma), testicular and thyroid ultrasound, and UFC and serum IGF-1 levels. For pre-pubertal pediatric patients, we recommend annual echocardiogram (biannually for patients with a history of excised myxoma) and testicular ultrasound for boys. If close monitoring of growth rate and pubertal staging indicates other abnormalities, such as possible Cushing syndrome appropriate testing should be done as needed. For PPNAD leading to Cushing syndrome, in addition to UFC we recommend diurnal cortisol levels (11.30 pm, 12.00MN and 7.30 am, 8.00 am sampling) and/or dexamethasone-stimulation test (modified Liddle's test, as per Stratakis et al. [10]), and adrenal computed tomography. For gigantism/acromegaly, in addition to serum IGF-1 levels, pituitary magnetic resonance imaging and a 3-hour oral glucose tolerance test (oGTT) may be obtained. For psammomatous melanotic schwannoma, magnetic resonance imaging of the brain, spine, chest, abdomen, retroperitoneum, and/or pelvis may be necessary (21,22).

Clinical and biochemical screening for CNC remains the gold standard for the diagnosis of CNC. Molecular testing for *PRKARIA* mutations is not recommended at present for all patients with CNC, but may be advised for detection of affected patients in families with known mutations of that gene to avoid unnecessary medical surveillance of non-carriers.

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Figure 1.

Pigmentation in Carney complex; **A** and **B**: Lentigines on the vermillion border of the lips and the face; **C**: A blue nevus in a patient with the complex **D** and **E**: Other patients with Carney complex (and proven carriers of pathogenic *PRKARIA* mutations) have variable pigmentation; some (like the patient in **F**) have very little and one has to look for other signs of the complex, such as a skin myxoma in the nipple area (**G**).

Figure 2.

Pigmentation in Carney complex; **A:** Café-au-lait spots are frequent in Carney complex but they tend to be smaller than in the neurofibromatosis and McCune-Albright syndromes. **B** and **C:** nevi or lentigines may be present in unusual and not necessarily sun exposed locations, such as here on the ear and the penis. Genital macules are frequent in both male and female patients with Carney complex.

Table 1Clinical manifestations of Carney complex *at the time of presentation.*

Manifestation	Number of patients	Percentage
Spotty skin pigmentation	262	77
Heart myxoma	178	53
Skin myxoma	110	33
PPNAD *	88	26
LCCSCT *	42	33 (of male patients)
Acromegaly	33	10
PMS *	33	10
Thyroid nodules or cancer	11	5
Breast ductal adenoma	6	3 (of female patients)

* *Abbreviations* PPNAD = primary pigmented nodular adrenocortical disease; LCCSCT = large-cell calcifying Sertoli cell tumor; PMS = psammomatous melanotic schwannoma

Table 2

Diagnostic criteria for Carney complex

To make a diagnosis of Carney complex, a patient must either: 1) exhibit two of the manifestations of the disease listed below, or 2) exhibit one of these manifestations and meet one of the supplemental criteria (an affected 1 st -degree relative or an inactivating mutation of the <i>PRKARIA</i> gene)	
1	Spotty skin pigmentation with a typical distribution [lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa]
2	Myxoma (cutaneous and mucosal) *
3	Cardiac myxoma *
4	Breast myxomatosis * <i>or</i> fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis ^a
5	PPNAD * <i>or</i> paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test ^b
6	Acromegaly due to GH-producing adenoma *
7	LCCSCT * <i>or</i> characteristic calcification on testicular ultrasonography
8	Thyroid carcinoma * <i>or</i> multiple, hypoechoic nodules on thyroid ultrasonography
9	Psammomatous melanotic schwannoma *
10	Blue nevus, epithelioid blue nevus (multiple) *
11	Breast ductal adenoma (multiple)
12	Osteochondromyxoma of bone *
Supplemental criteria:	
1	Affected 1 st -degree relative
2	Inactivating mutation of the <i>PRKARIA</i> gene

* with histologic confirmation,

^a see reference 6,

^b see reference 7