

## Case Report

# A Case of Familial Carney Complex

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## Abstract

Carney complex is a syndrome characterized by skin pigmentation abnormalities, myxomas, endocrine tumors/overactivity, and schwannomas. It is caused by a mutation in the PRKAR1A gene that encodes the enzyme protein kinase A regulatory subunit type 1 alpha. A 23-year old male was diagnosed with Carney complex on the basis of spotty skin lentigines on his face and lips, multiple thyroid neoplasms, a right ventricular myxoma, and bilateral testicular tumors. A total bilateral orchectomy was performed and the pathological findings revealed Leydig's cell tumors on one side and a Sertoli cell tumor on the other side. When his first-degree relatives were examined, his mother was found to have Carney complex as well. This is the first reported case of familial Carney complex in China.

**Keywords:** Carney complex, Leydig's cell tumors, myxomas, PRKAR1A gene, schwannomas, Sertoli cell tumors, skin lentigines

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## Introduction

Carney complex (CNC), first reported by Carney, et al. in 1985, is a relatively rare autosomal dominant inherited disease. Clinically, CNC presents as a complication of spotty skin pigmentation (lentigines), cardiac and cutaneous myxomas, schwannomas and endocrine neoplasms. CNC affects both sexes equally and has two known genotypes: a mutation of the tyrosine kinase PRKAR1A gene located on 17q23-24 and several mutations located on 2p16.

In this article, we describe the relevant diagnostic criteria for familial Carney complex, the symptoms of which can be easily mistaken for those of other disorders. We almost missed this diagnosis because Carney complex is rare; therefore our case report emphasizes both the classic presenting symptoms of the complex and the differential diagnoses that might cloud a clinician's judgment. We believe this is the first case of familial Carney complex in China.

## Case Report

A 23-year-old male presented with bilateral testicular nodules confirmed by CT scan (Figure 1). He was diagnosed with Carney complex on the basis of intense spotty lentigines on his face (Figure 2), multiple subcutaneous nodules around the eyes, a cardiac myxoma in the right ventricular chamber, and multiple thyroid neoplasms. There was no history of diabetes or hypertension.

A total bilateral orchectomy was performed, and pathological examination revealed Leydig's cell tumors in the right testicle and Sertoli cell tumors in the left testicle (Figure 3).

Echocardiography documented a mass in his right ventricle near the tricuspid valve (Figure 4). This mass was suspicious for

cardiac myxoma but did not cause a functional tricuspid obstruction. A cardiac tumor resection was performed and intraoperative findings showed a pedunculated myxoma that had adhered to the chordae tendineae of the tricuspid valve. Pathological findings indicated myxoma with no malignancy.

A thyroid ultrasound and CT scans of the pituitary and adrenal glands were carried out. The ultrasound showed multiple thyroid nodules, some of which were cystic and solid. The pituitary and adrenals appeared normal. The patient had elevated levels of FSH, LH, PRL, and hCG. Other laboratory tests, including thyroid function, TSH, and a complete blood count, showed no abnormalities.

When the patient's family member were evaluated, his father and brother were normal but his mother was found to have multiple thyroid neoplasms, cutaneous myxomas (multiple nodules on her nipples and subcutaneous tumors on her back), a recurrent myxoma in the left atrium of her heart, and spotty facial freckling. She had undergone open-heart surgery for cardiac myxomas at ages 27 and 42. MRI confirmed infarctions in the frontal lobes, lobi temporalis, parietal lobes, and basal ganglia, which caused by embolus from recurrent cardiac myxoma. A1 obstructions in the arteriaecerebri media and arteriaecerebri anterior were discovered by MRI cerebral angiography. An EKG revealed that a myocardial infarction had taken place. A CT scan of the coronary arteries showed aneurysmal dilatation at the junction of the left anterior descending artery and the diagonal branch crotch. Ultrasounds revealed multiple thyroid adenomas and one subcutaneous tumor on her back. Her systemic examination revealed multiple nodules on her nipples and freckling on her lips and face.

Because both mother and son exhibited classic symptoms of the disorder, we diagnosed familial Carney complex.

## Discussion

Carney complex, which was first reported in 1985 by Carney, et al. is a rare autosomal dominant genetic disorder that can present with myxomas (heart, skin, and breast), spotty skin pigmentation (lentigines and blue nevi), endocrine tumors (adrenal, testicular, pituitary), and peripheral nerve tumors (schwannomas). Many different combinations of symptoms in this disorder can make a

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Figure 1. Multiple high densities in the patient's left testicle.



Figure 2. Lentiginos on the patient's face and lips.

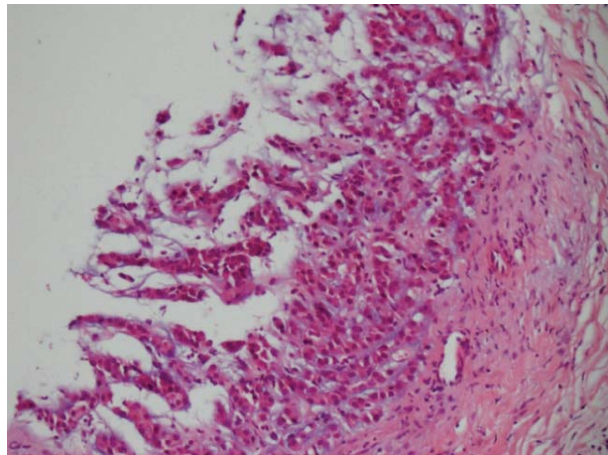


Figure 3. Pathological examination showing a Sertoli cell tumor (H&E  $\times 10$ ).

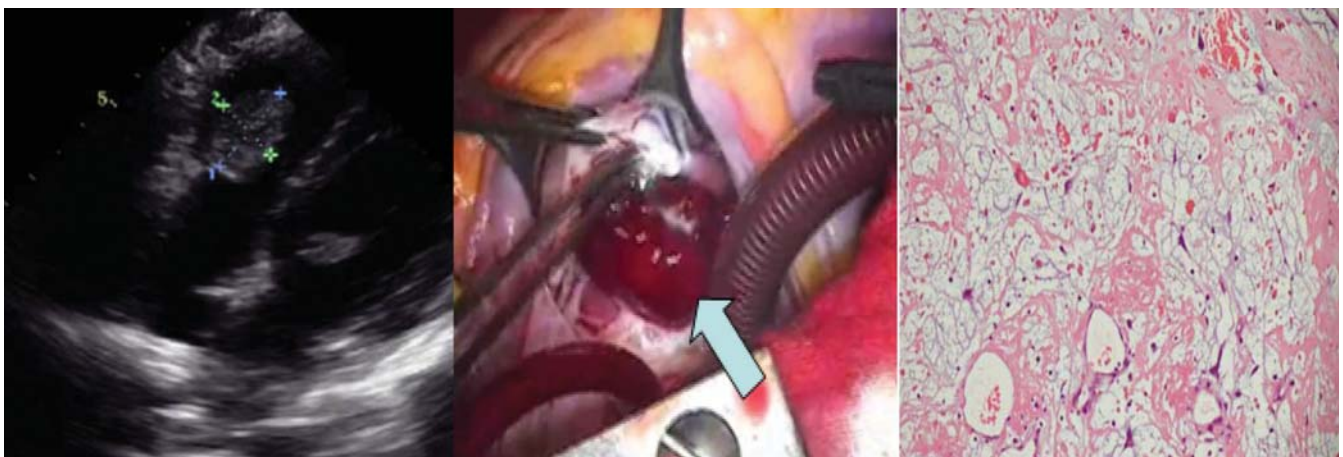


Figure 4. Right ventricular tumor which was myxoma with no malignancy conformed by pathological examination (H&E  $\times 10$ ).

**Table 1.** Diagnostic Criteria for CNC

❖	<b>Major diagnostic criteria</b>
•	Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
•	Myxomas (cardiac, cutaneous and mucosal)
•	Breast myxomatosis or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
•	PPNADs or paradoxical positive response of urinary glucocorticoid excretion to dexamethasone administration during Liddle's test
•	Acromegaly due to GH-producing adenomas
•	LCCSCTs or characteristic calcifications on testicular ultrasound
•	Thyroid carcinomas or multiple, hypoechoic nodules on thyroid ultrasound in a young patient
•	Psammomatousmelanoticschwannomas
•	Blue nevi, epithelioid blue nevis
•	Breast ductal adenomas
•	Osteochondromyxomas
❖	<b>Supplemental criteria</b>
•	Affected first-degree relative
•	Inactivating mutation of the PRKARIA gene
❖	<b>Findings suggestive of CNC but not diagnostic for the disease</b>
•	Intense freckling (without darkly pigmented spots or typical distribution)
•	Blue nevis, common type (if multiple)
•	Café-au-lait spots or other "birthmarks"
•	Elevated IGF-I levels, abnormal GTT, or paradoxical GH response to TRH testing in the absence of clinical acromegaly
•	Cardiomyopathy
•	Pilonidal sinus
•	History of Cushing's syndrome, acromegaly, or sudden death in extended family
•	Multiple skin tags or other skin lesions; lipomas
•	Colonic polyps (usually in association with acromegaly)
•	Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)
•	Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected on ultrasound)
•	Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors

proper diagnosis difficult.

A diagnosis of CNC is made when two or more major hallmarks of the disease are present at the same time. A number of related clinical components may suggest CNC, but are not considered diagnostic for the disease (Table 1).<sup>1,2</sup> Alternatively, the diagnosis may be made if one major criterion is present and a first-degree relative has CNC or an inactivating mutation of the gene encoding the protein kinase A regulatory subunit 1 $\alpha$  (PRKARIA).<sup>3</sup> One study from the Mayo Clinic compared patients with sporadic myxoma with CNC patients. The patients with CNC were younger than 40 and had unusual skin freckling (68%), associated with benign, non-cardiac myxomatous tumors (57%), endocrine neoplasms (30%), and a high frequency of familial cardiac myxoma (25%), as well as familial endocrine tumors (14%).<sup>4</sup>

#### Endocrine tumors

Large cell calcifying Sertoli cell tumors and Leydig's cell tumors are the testicular tumors found in Carney complex. In our case, both tumors were present, which is rare. Excisional biopsy or surveillance are the treatment options for bilateral testicular tumors in Carney complex.<sup>5</sup>

The most common endocrine gland manifestation in CNC pa-

tients is ACTH-independent Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD).<sup>6</sup> However, our patient's adrenal examination showed no abnormalities. Thyroid ultrasounds showed multiple neoplasms in both lobes of the thyroid in mother and son, some of which were cystic and solid. Thyroid nodules occur in up to 75% of CNC patients. Growth hormone-secreting pituitary hyperplasia and adenomas, neither of which occurred in our patients, can produce the biochemical hallmarks of acromegaly.

Elevated insulin-like growth factor 1 and growth hormone levels as well as subtle hyperprolactinemia can be present in up to 75% of CNC patients.<sup>7</sup> However, both of our patients' pituitary examinations were negative. Psammomatous melanotic schwannomas are rarely seen in any condition, but when they occur they are found in the central nervous system, the gastrointestinal tract, and along the paraspinal sympathetic chain. No psammomatous melanotic schwannomas were found in our patients.

#### Cardiac myxomas

Cardiac myxomas are not a consistent finding in CNC, but are responsible for over 50% of CNC deaths because they impair cardiac output and cause embolic events.<sup>8</sup> The majority of cardiac

myxomas occur sporadically as isolated lesions in the left atrium of middle-aged women. However, in CNC they can present in a variety of ways. A total of 127 cardiac myxomas surgically resected at Mayo Clinic from 110 individuals were studied by Maleszewski.<sup>9</sup> Familial cardiac myxomas and the sporadic type differed in location (atrium: 87% vs. 100%, respectively; ventricle 13% vs 0%, respectively); number (single tumors 50% vs 99%, respectively; multiple tumors 50% vs 1%, respectively); and recurrence (18% vs 0%, respectively).

The principal clinical manifestation of this tumor is intracardiac obstruction, followed by extracardiac embolism, and general symptoms including fever, myalgia, and arthralgias. Many clinicians recommended that individuals under the age of 40 years with a cardiac myxoma in the left atrium should be evaluated for Carney complex. CNC myxomas are usually in the left atrium, with only 2.5% to 6% occurring in the right ventricle. The myxoma that originated in the tricuspid chordae tendineae in our patient is rarely seen. Echocardiography using the transesophageal approach finds intracardiac tumors with 100% sensitivity and should be used in this setting.<sup>10</sup> Complete tumor excision with close follow-up is the best treatment for cardiac myxomas.

#### Cutaneous myxomas

In one study, 13 of 16 patients (81%) with cardiac myxomas also had cutaneous myxomas which were diagnosed prior to the cardiac neoplasms. CNC cutaneous myxomas are notable for an early appearance (mean age 18 years), multiple locations (71% of patients), small size (usually less than 1 cm in diameter), a tendency to recur, and widespread distribution with a predilection for certain sites (eyelids, ears, nipples, and perineum).<sup>11</sup> Patients presenting with cutaneous myxomas with these characteristics should be evaluated for Carney complex.

#### Mucocutaneous pigmentation

Mucocutaneous pigmentation is the most common clinical manifestation of CNC. Lentiginos appear in typical distribution, including the border of the lips, the eyelids and elsewhere on the face, the ears and the genitals. According to one study that involved 58 CNC patients, spotty facial pigmentation was present in 36 subjects (62%). Twenty-nine subjects (50%) also had pigmented spots on their lips.<sup>12</sup> This type and distribution of pigmentation should alert clinicians to the possible presence of CNC; therefore both patients and first degree relatives should be evaluated for the problem.

#### Embolicism

One of clinical features of cardiac myxoma is extracardiac embolism that causes cerebral and peripheral vascular obstructions. Villous surface myxomas, myxomas accompanied by cardiac arrhythmias, lobulated myxomas, hemorrhagic and necrotic myxomas, as well as large volume tumors are related to embolicism. Xiajian points out that the arteriaecerebri media are principally affected. Nuclear spin tomography and echocardiographic cinemode sequences provide useful images of potential embolicisms. Clinical manifestations include facioplegia, monoplegia, hyper-spasmia, hemiplegic paralysis, logagnosia, and disorders of consciousness.<sup>13</sup>

In our patients, the mother suffered from arteriaecerebri media obstruction and her EKG showed a v1 v2 v3 lead q wave, which implied that a myocardial infarction had taken place. A coronary CTA showed aneurysmal dilatation at the junction of the left an-

terior descending artery (LAD) and the diagonal crotch between the LAD's branches.

Aneurysms develop, due to the continuous growth of the myxomas causes deterioration of vascular walls.<sup>14</sup> Interestingly, spontaneous recanalization of obstructed coronary vessels often occurs in atrial myxomas.<sup>15</sup> In our case, it occurred in the mother. The connection between coronary aneurysms and myxomas needs further research.

#### Genetic analysis

Inactivating mutations in the PRKAR1A gene that encodes the PKA type I alpha regulatory subunit (RI $\alpha$ ) are responsible for nearly 98% of the cases of Carney complex.<sup>16</sup> Two-thirds of CNC-associated cardiac myxomas exhibit mutations in PRKAR1, but no PRKAR1 mutation is detected in 30% of patients.<sup>9</sup> CNC patients with PRKAR1A mutations develop cardiac myxomas, cutaneous myxomas, thyroid tumors, and gonadal tumors at an earlier age compared to CNC patients that did not have PRKAR1A mutations.<sup>17</sup>

Recent evidence has shown that dysregulation of the cAMP/PKA pathway caused by PRKAR1A mutations can modulate other signaling pathways and contribute to the development of adrenocortical tumors.<sup>18</sup>

Genetic linkage analysis reveals two different loci for CNC: on chromosomes 2p16 and 17q22-24.<sup>19,20</sup> To date, more than 120 disease-causing PRKAR1A mutations have been reported in Carney complex patients.<sup>21</sup> The majority of CNC-causing PRKAR1A mutations are base substitutions, small deletions, and insertions or rearrangements.<sup>1</sup> Large PRKAR1A deletions can occur, but they are rare.<sup>22</sup>

Genetic diagnosis allows for more appropriate and effective therapeutic strategies and also eliminates the need for unnecessary tests for people carrying the gene. If the gene test is positive, relatives can avoid the laboratory examinations and imaging studies. Regrettably, genetic analysis was not performed on our patients.

In conclusion, first we thought that our patient's cardiac tumor was a metastasis from his testicular neoplasms, but his other problems warranted further investigation. After studying the literature about Carney complex, we realized our patient's symptoms fit this diagnosis and examination of his first-degree relatives confirmed our suspicions. This case highlights the importance of knowing other common features of Carney complex, therefore a proper diagnosis can be made and effective treatment can be instituted.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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