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The Spectrum of Thyroid Gland Pathology in Carney Complex: The Importance of Follicular Carcinoma

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Abstract

The initial description of Carney complex (CNC) in 1985 included myxomas, spotty skin pigmentation, and endocrine overactivity (of the adrenal, the pituitary, and the testis). In 1997, thyroid neoplasms were found in 3 patients with CNC and involvement of the gland in the syndrome was apparent. Herein, we describe the clinical, pathologic, and follow-up findings in 26 patients with CNC and a disorder of the thyroid gland. The patients were predominantly middle-aged women with an asymptomatic thyroid mass. Four patients had hyperthyroidism, which was caused by follicular hyperplasia in 2 patients and by toxic adenoma in 2 others. Pathologic findings included benign lesions (follicular hyperplasia, nodular hyperplasia, and follicular adenoma) in 16 patients and carcinomas (follicular or papillary) in 10 patients. The follicular carcinomas had unusual features, multifocality, bilaterality, and lymph node metastasis. The tumor was fatal in 3 of 4 patients with a tumor 3 cm or greater in diameter. One patient had an unusual multifocal microscopic follicular hyperplasia. Detection and treatment of the thyroid neoplasms in patients with CNC requires long-term follow-up of patients with the syndrome.

Keywords

Carney complex; pathology; thyroid; thyroid neoplasms

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Introduction

In 1985, Carney et al (1,2) described the dominantly inherited multitumor syndrome of myxomas, spotty skin pigmentation, and endocrine overactivity, now referred to as Carney complex (CNC). Later, psammomatous melanotic schwannoma, epithelioid blue nevus, and osteochondromyxoma of bone were added to the syndrome (3-5). The tumors were infrequent or rare and multifocal in the organ or system affected. Endocrine overactivity resulted from adrenal, pituitary, and testicular hyperplasia and neoplasia.

In 1997, Stratakis and colleagues (6) reported tumors of the thyroid gland in 3 of 53 patients (6%) with CNC: 1 patient had papillary carcinoma, 1 had follicular carcinoma, and 1 had follicular adenoma. The tumors were multiple in 2 patients. These findings showed that thyroid tumors were part of the syndrome. In 2009, Bertherat et al (7) found a thyroid disorder in 88 of 353 patients with CNC (25%); papillary or follicular carcinoma or both occurred in 9 of the 353 patients (2.5%). One patient died of follicular carcinoma. The present investigation was undertaken to study the pathologic findings in the thyroid gland in CNC.

Patients and Methods

This study was approved by the Mayo Clinic Institutional Review Board (protocol 979-01). The clinical and pathology records of Mayo Clinic in Rochester, Minnesota, J.A.C.'s files, and records of the National Institutes of Health (NIH) (Bethesda, Maryland) from January 1999 through June 2016 were searched for patients with CNC who had thyroid gland surgery or who likely had thyroid gland pathology because of thyroid symptoms (thyrotoxicosis). Patient CNC-associated findings and thyroid-related clinical, surgical, and pathologic findings and follow-up information were abstracted from the records. A second search of those records was conducted for patients with CNC and normal thyroid clinical findings who had died of nonthyroid-related causes and whose thyroid gland was available at autopsy for histologic study. The world medical literature from January 1999 through June 2016 was searched for reports of patients with CNC and mention of the thyroid gland.

For the patients identified in the searches, the available thyroid surgical and autopsy histologic slides, pathology reports, and paraffin blocks were obtained. Sections 4 μ m thick were cut for hematoxylin-eosin staining, and immunostaining with antibodies was directed against the following: thyroglobulin (Ultraview, CC1, 1/100; Cell Marque, 2H11/64E1); mesothelial cell (HBME-1) (Refine, ER2, 1/40; Dako, HBME-1); cytokeratin 19 (Ultraview, CC1, 1/20; Dako, RCK108); galectin-3 (Ultraview, CC1, 1/75; Leica [Novocastro], 9C4); PAX8 (Optiview, CC1, 1/50; Biocare, BC12); TTF-1 (Ultraview, CC1, 1/700; Dako, 8G7G3/1); and calcitonin (Ultraview, 1/4,000; Dako, polyclonal). The controls were as follows: for thyroglobulin, thyroid (positive) and testis and placenta (negative); for mesothelial cell, thyroid tumor (positive) and normal thyroid (negative); for cytokeratin 19, small intestinal epithelium (positive) and colon and tonsil (negative); for galectin-3, tonsillar macrophages (positive) and tonsillar mantle zone (negative); for PAX8, normal kidney (positive) and kidney stromal cells (negative); for TTF-1, thyroid (positive) and placenta and

testis (negative); and for calcitonin, medullary thyroid carcinoma (positive) and normal thyroid (negative).

Results

Clinical

The first search identified 10 patients with CNC who had or likely had thyroid gland pathology (8 women and 2 men; 3 were in Mayo Clinic records, 5 were in J.A.C.'s files, and 2 were in the NIH files). Two patients who had Graves disease and a third who had a nodule that caused thyrotoxicosis were presumed to have thyroid pathology. Patient sex, age at diagnosis of CNC, age at diagnosis of a thyroid disorder, CNC components, and *PRKARIA* mutational status are shown in Table 1. Patients 5 and 8 were mother and daughter. Patient 9 was described previously (6,9) and is included in the present study because of unusual pathologic features of the thyroid and availability of follow-up.

Clinical thyroid findings, results of thyroid ultrasonography and fine-needle aspiration biopsy studies, preoperative diagnosis, treatment, and pathologic diagnosis for the 10 patients are shown in Table 2. Patients 3, 6, and 7 had thyrotoxicosis and were treated medically. The thyroid lesions were found in all patients except patient 2 after a diagnosis of CNC was established.

Pathologic findings in the 10 patients included follicular carcinoma (3 patients), follicular adenoma (3 patients, presumed in patient 7), nodular hyperplasia (1 patient), and diffuse follicular hyperplasia (presumed in 2 patients) (Table 2). None of the patients had C-cell disease. Findings and follow-up for patients 1, 4, and 9, who had follicular carcinoma, are shown in Table 3.

Of the 169 literature abstracts identified, 17 (10%) described 18 patients with a thyroid abnormality. The patients' sex, age, CNC components, *PRKARIA* mutational status, and thyroid pathologic diagnosis are shown in Table 4. Of these 18 patients, 15 were asymptomatic, and the thyroid lesions were found on physical examination. One patient (patient 11) had thyrotoxicosis caused by a toxic adenoma; a subtotal thyroidectomy was performed, and 5 years later a follicular carcinoma was found. Another 47 patients (28%) described in the abstracts had normal results on thyroid clinical or sonographic studies. The gland was not referred to in the remaining 105 abstracts (62%).

The second search identified 6 patients with CNC who had clinically normal thyroid glands and died of nonthyroid related causes; thyroid glands obtained at autopsy were normal histologically (Table 5).

Pathology

Gross and microscopic findings of lesions and follow-up for patients 1, 4, and 9 are presented in Table 3 along with findings from another 4 patients with follicular carcinoma reported in the literature. Histologic findings in patient 4 are presented in Figure 1. Immunostaining of the carcinomas in patients 1, 4, and 9 showed cytoplasmic positivity for thyroglobulin (3 of 3 tumors), nuclear positivity for PAX8 (3 of 3), nuclear positivity (50%

of cells) for HBME-1 (2 of 3 tumors), scattered cells positive for galectin-3 (3 of 3), and no staining with cytokeratin 19 and calcitonin (3 of 3 tumors).

Mutational findings and pathologic diagnoses in the 16 reported patients are shown in Table 4. Microscopic findings in patient 22 were unusual. The patient, a 13-year-old girl, had a total thyroidectomy for an asymptomatic multinodular goiter (21). The pathology report mentioned a 1.5×1×1-cm tumor. The diagnosis was “multifocal papillary and follicular hyperplasia, atypical.” Review of the histologic findings revealed a multinodular goiter, follicular adenoma, and microscopic follicular adenomatosis (Figure 2).

Discussion

The components of CNC have emerged over time. Thyroid involvement in the syndrome was reported in 1997 (6), 12 years after the first description of CNC (1), and confirmed more than a decade later (7). Herein, we have described the clinical, pathologic, and follow-up findings for 26 patients with CNC who had thyroid gland surgery (Tables 1-4 and 6) (including the thyroid adenoma found at autopsy in patient 20). Of the 10 patients identified from the records of Mayo Clinic, J.A.C., and the NIH, 6 had thyroid-related symptoms and 4 had thyrotoxicosis (Table 2). Of the 16 patients identified from the literature search, 15 were asymptomatic.

The results of the combined study and literature findings showed that a thyroid disorder was an uncommon and late-developing feature of CNC. Most of the patients were asymptomatic women; the female to male ratio was approximately 2:1. The patients ranged in age from the second through the sixth decades. The youngest and oldest at operation were 13 and 57 years, respectively; the mean age was 34 years.

Pathologic findings included 1) follicular carcinoma (7 patients, multiple tumors in 2); 2) papillary carcinoma (3 patients); 3) follicular adenoma (7 patients; 1 [patient 22] also had a multinodular goiter and multifocal microscopic papillary and follicular adenomatosis) (Figure 2); and 4) nodular hyperplasia (5 patients). Three patients with hyperthyroidism (patients 3, 6, and 7) did not undergo surgery (2 had Graves disease and 1 had a toxic nodule). Patient 11 had a toxic follicular adenoma at age 54 years; a follicular carcinoma was found 5 years later.

Follicular carcinoma was the most serious lesion encountered in the study. Most of the affected patients were middle-aged (mean age, 46 years; range, 22-59 years). Tumors in 4 patients were large (≥ 3 cm in diameter) at discovery and had already metastasized. The neoplasm was multifocal in patients 1 and 9. Clinically, thyroid malignancy was suspected in patients 1 and 4. The tumors that metastasized were 3 cm or larger in diameter. The neoplasm was fatal in 3 of the 7 patients (Table 3).

Follicular carcinoma accounts for about 20% of all thyroid carcinomas (30). Typically, it is a single, slow-growing tumor. Lymph node metastasis is found in less than 10% of cases (30). Thus, finding the tumor with multifocal and bilateral occurrence and with lymph node metastasis was unexpected and hardly happenstance. The metastases were not responsive to radioiodine (¹³¹I) or lenvatinib (a multiple kinase inhibitor that inhibits vascular endothelial

growth factor receptors). Papillary carcinoma occurred in 3 patients. Curiously, the follicular tumor was the more common of the 2 carcinomas, the reverse of the frequency in the general population.

Four patients had thyrotoxicosis caused by diffuse follicular hyperplasia (presumed in patients 3 and 6) and follicular adenoma (patient 11 and presumed in patient 7). Transient thyrotoxicosis occurred in a patient with CNC not included in the study (31). Interestingly, ablation of thyroid-specific *PRKARIA* in mice resulted in follicular carcinoma and hyperthyroidism (32).

As has been described, several benign and malignant follicular lesions occurred among the 26 patients. This is the multilesional pattern found in the adrenal and testis in CNC; primary pigmented nodular adrenocortical disease, cortical adenoma, and cortical carcinoma occur in the adrenal, and Leydig cell hyperplasia, Leydig cell tumor and Leydig cell carcinoma occur in the testis (29,33). Also, the thyroid lesions were functional and nonfunctional, as are those in the adrenal and testis.

The results indicate the importance of investigating any thyroid nodule in patients with CNC, particularly a nodule larger than 1 cm. The follicular carcinoma in patient 12 measured 1.5 in diameter. More patients with CNC and a thyroid lesion will need treatment as they reach their fourth decade and beyond. Some will have follicular carcinoma, some will have papillary carcinoma, and an exceptional patient will have both tumors (7).

CNC joins the small group of dominantly inherited diseases, including Cowden disease and hereditary familial polyposis, in which nonmedullary thyroid neoplasia occurs. Cowden disease is part of the *PTEN* hamartoma tumor syndrome caused by heterogeneous mutation of the gene located on chromosome 10q23. Hereditary familial polyposis results from mutation of the *BMPRIA* gene also located on chromosome 10q23. Both disorders include thyroid tumors; follicular thyroid cancer is more common than papillary.

Early detection and surgical resection of follicular and papillary carcinomas offers the best hope of cure. Long-term surveillance of CNC patients is required to detect thyroid carcinomas at an early and curable stage. Clinical or sonographic examination of the gland at annual or biennial cardiac echocardiographic evaluations should improve detection of the lesions.

In summary, we report the clinical and pathologic findings in the thyroid gland of 26 patients with CNC. The findings 1) showed that follicular carcinoma was the most serious lesion affecting the gland in the syndrome; 2) described unusual features of the carcinomas; 3) added follicular hyperplasia (Graves disease) to the pathologic lesions; 4) mentioned a possibly unique type of microscopic multifocal follicular hyperplasia; and 5) added thyrotoxicosis to the clinical findings in the syndrome. Long-term surveillance of patients with CNC is necessary to detect and treat the thyroid lesions, particularly the carcinomas.

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Abbreviations

CNC	Carney complex
HBME-1	mesothelial cell antibody
NIH	National Institutes of Health

Figure 1.

Follicular Carcinoma (Patient 9). A, Solid tumor with a thick, fibrous capsule invaded by tumor. B, Capsular intravascular tumor thrombus. C, Tumor cells arranged in a coarse alveolar and trabecular pattern. D, Sheet of relatively small cells with eosinophilic cytoplasm and regular hyperchromatic nuclei. E, Circumscribed follicular adenoma featuring large and small follicles. F, Globular cytoplasmic positivity for thyroglobulin with unstained nuclei (left) and nuclear positivity for PAX8 (right). (A-E, Hematoxylin-eosin.)

Figure 2. Follicular Adenomatosis (Patient 22). Low-power image of extratumoral thyroid showed multiple capsulated and unencapsulated microfollicular and macrofollicular lesions (arrows) in normal colloid thyroid.

Table 1
Demographic and Clinical Features of 10 Patients With CNC and Thyroid Tumor or Thyrotoxicosis

Patient ^a	Sex	Age at Diagnosis, y		Thyroid Lesion	CNC Components		Germline <i>PRKARIA</i> Mutation
		CNC					
1	Female	43	54		Lentiginos, PPNAD, cardiac and cutaneous myxomas		Present
2	Female	34	18		Cardiac myxoma, pituitary adenoma (acromegaly), pilonidal cyst		Not tested
3 (8)	Female	38	43		Lentiginos, PPNAD, neural nasal tumor, bilateral ovarian carcinoma, thyrotoxicosis		Absent
4	Female	27	43		Lentiginos, cutaneous and cardiac myxomas, blue nevus, pituitary adenoma (acromegaly)		Present
5	Female	16	14		Cardiac and mammary myxomas, PPNAD		Absent
6	Female	21	17		Lentiginos, cardiac myxoma, thyrotoxicosis		Present
7	Male	54	54		Lentiginos, cutaneous myxoma, PMS, thyrotoxicosis		Not tested
8	Female	16	17		Lentiginos, cardiac and mammary myxomas		Absent
9 (6,9)	Female	30	30		Lentiginos, cutaneous and cardiac myxomas, blue nevus, pituitary adenoma (acromegaly)		Present
10 (10)	Male	9	12		Lentiginos, cutaneous myxoma, LCCSCT		Present

Abbreviations: CNC, Carney complex; LCCSCT, large-cell calcifying Sertoli cell tumor; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

^aReferences are cited in parentheses.

Clinical Findings, Laboratory Testing Results, Preoperative and Pathologic Diagnoses, and Therapy for 10 Patients With CNC and Thyroid Tumor or Thyrotoxicosis

Table 2

Patient ^a	Symptoms, Clinical Findings	Ultrasonography	Fine-Needle Aspiration Biopsy	Preoperative Diagnosis	Treatment	Pathologic Diagnosis
1	Patient felt a neck swelling Enlarged nodular thyroid	Not done because of clinical diagnosis of carcinoma	Not done because of clinical diagnosis of carcinoma	Thyroid carcinoma	Near total thyroidectomy and cervical lymphadenectomy CyberKnife for pulmonary metastases	Follicular carcinoma Chronic lymphocytic thyroiditis
2	Symptom information not available Colloid goiter	Not available at presentation	Not available at presentation	Multinodular thyroid	Subtotal thyroidectomy	Nodular hyperplasia
3 (8)	Classic symptoms of Graves disease Diffusely enlarged thyroid	Not done because of clinical diagnosis of Graves disease	Not done	No surgery (Graves disease)	Medical	None (presumably diffuse follicular hyperplasia)
4	Patient felt neck enlargement Firm, mobile, 4-cm left thyroid mass	4.6×3×3.2-cm heterogeneous mass with coarse calcification	Hürthle cell lesion	Thyroid carcinoma	Total thyroidectomy Radioiodine (¹³¹ I) and lenvatinib treatment of pulmonary metastases was ineffective	Follicular carcinoma
5	No symptoms Left thyroid mass	2-cm solid nodule	Not done	Benign thyroid nodule	Left lobectomy	Follicular adenoma
6	Classic symptoms of Graves disease Diffuse, asymmetric thyroid enlargement	Not done because of clinical diagnosis of Graves disease	Not done	No surgery (Graves disease)	Medical	None (presumably diffuse follicular hyperplasia)
7	Symptom information not available Hyperthyroidism and thyroid nodule	No information	No information	No surgery (toxic nodule)	Medical	None (presumably follicular adenoma)
8	Intermittent dyspnea Thyroid nodule	Not done	Benign thyroid nodule	Left thyroid mass	Left lobectomy	Follicular adenoma
9 (6,9)	Occasional throbbing in neck Slightly tender right thyroid mass	Right lobe: 2-cm inhomogeneous hypoechoic nodule; 2 additional nodules, 0.4 and 0.6 cm Left lobe: 0.8-cm hypoechoic nodule	Not done	Multinodular goiter	Total thyroidectomy Postoperative radioiodine (¹³¹ I)	Follicular carcinoma
10 (10)	None	6-mm solid hypoechoic nodule	Suggestive of Hürthle cell neoplasm	Hürthle cell neoplasm	Right hemithyroidectomy	Hürthle cell nodule

Abbreviation: CNC, Carney complex.

^aReferences are cited in parentheses.

Table 3
Pathologic Findings in the Thyroid Gland, Metastasis, and Follow-up of 7 Patients With
CNC and Follicular Carcinoma

Patient ^a	Findings			
	Gross	Microscopic	Metastasis	Follow-up
1	Gland weighed 94 g Left lobe: Greyish-white, 6.5-cm tumor Right lobe and isthmus: 1-cm lesion in each; right lobe tumor was cystic	Left lobe: Tumor composed of 1) sheets of small eosinophilic cells in a trabecular pattern and with microfollicular differentiation and 2) sheets of larger cells with weakly eosinophilic cytoplasm and follicular differentiation; lesion penetrated tumor capsule; extensive vascular invasion of tumor capsule Right lobe and isthmus: tumors histologically similar to left lobe tumor	Cervical lymph nodes at primary surgery Pulmonary 2 y after thyroidectomy	Dead at age 63 y
4	Gland weighed 54 g Left lobe: Well-demarcated, 4.2-cm, partially encapsulated, white-tan to red, focally hemorrhagic lesion Right lobe: Normal	Left lobe: Tumor featured oncocytic cells in solid and trabecular pattern with infiltrative growth effacing a partial tumor capsule; extrathyroidal extension and extensive lymphatic and vascular invasion; infiltration of 2 ipsilateral parathyroid glands Right lobe and isthmus: normal	Pulmonary at presentation	Dead at age 44 y
9 (6,9)	Gland weight not available Right lobe: 3-cm yellow-brown mass with white capsule and a 0.5-cm soft brown lesion with a thick white capsule Left lobe: 0.4-cm yellow-brown soft lesion	Right lobe: Large lesion composed of sheets of polygonal to cuboidal oncocytic cells and occasional colloid-containing follicles; cells were moderately pleomorphic, with increased nuclear to cytoplasmic ratio; enlarged nucleoli, and common mitotic figures; second lesion was histologically similar Left lobe: follicular adenoma	Pretracheal and paratracheal lymph nodes and pulmonary 2 y after thyroidectomy	Dead at age 39 y
11 (11)	Gland weight not available Lobe 1: yellowish-brown, 5×5×3.5-cm nodule Lobe 2: encapsulated, 4×3×1.5-cm tumor	Lobe 1: encapsulated adenoma with variously sized follicles, some with a mucin content Lobe 2: tumor composed of cuboidal cells, some pleomorphic, arranged in cords that infiltrated scarred connective tissue; follicles stained with alcian blue; capsular and vascular invasion was apparent	None	Dead at 64 y of cerebral infarction No follicular carcinoma at autopsy
12 (12)	Gland weight not available Right lobe: nodule surrounded by fibrous capsule Left lobe: not mentioned	Right lobe: tumor composed of cuboidal epithelial cells with moderate nuclear atypia and hyperchromasia and scattered bizarre cells arranged in solid and cordlike areas; capsular and microvascular invasion was apparent Left lobe: not mentioned	None	Alive No recurrence at age 59 y, 24 y after thyroidectomy
13 (13)	Gland weighed 26 g Left lobe: sharply outlined, 1.5-cm tumor with light-brown cut surface Right lobe: not mentioned	Left lobe: lesion composed of large polygonal oxyphilic cells with finely granular eosinophilic cytoplasm; cells arranged in small groups, forming follicles; moderate variation in nuclear size; lesion surrounded by a fibrous capsule of variable thickness; capsular and intracapsular vascular invasion was apparent Right lobe: not mentioned	None	Alive No recurrence at age 35 y, 13 y after thyroidectomy
14 (14)	Right lobe weighed 30 g	Right lobe: encapsulated, well-differentiated follicular tumor	None at primary surgery	Not available

Abbreviation: CNC, Carney complex.

^aReferences are cited in parentheses.

Demographic and Clinical Features and Pathologic Diagnosis of 16 Patients With CNC and Thyroid Pathologic Diagnosis

Table 4

Patient ^a	Sex	Age at Diagnosis, y		CNC Components	Pathologic Diagnosis
		CNC	Thyroid		
11 (11)	Female	64	54 and 59	PPNAD, cardiac myxoma	Toxic adenoma at age 54 y Follicular carcinoma at age 59 y
12 (12)	Female	53	35	Cardiac myxoma, PPNAD	Follicular carcinoma
13 (13)	Male	10	22	Cushing syndrome, PMS, LCCSCT	Follicular carcinoma and follicular adenoma
14 (14)	Female	19	19	Lentiginosis, cardiac and mammary myxomas	Follicular carcinoma
15 (15)	Female	31	19	Cutaneous and cardiac myxomas	Papillary carcinoma
16 (16)	Female	15	35	Cardiac and cutaneous myxomas, PMS	Papillary carcinoma
17 ^b (16)	Female	45	57	Cardiac myxoma	Papillary carcinoma
18 (17)	Male	21	42	Cardiac myxoma, PPNAD, lentiginosis	Follicular adenoma
19 (18)	Female	31	31	Cardiac myxoma, PMS	Follicular adenoma
20 (19)	Female	27	27	Cardiac and mammary myxomas, Cushing syndrome	Follicular adenoma
21 (20)	Female	20	40	LentiginosisAutopsy findings: PPNAD, mammary myxoma, dilated cardiomyopathy	Follicular adenoma (at autopsy)
22 (21)	Female	13	13	Lentiginosis, cutaneous and cardiac myxomas, malignant PMS	Follicular adenoma, microscopic papillary and follicular adenomatosis
23 (22)	Male	51	51	Lentiginosis, cardiac myxoma, pituitary adenoma (acromegaly)	Nodular hyperplasia
24 (23)	Male	32	35	Cardiac myxoma, pituitary adenoma, LCCSCT	Nodular hyperplasia
25 (24)	Male	46	46	Lentiginosis, cardiac myxoma, pituitary adenoma (acromegaly), LCCSCT	Nodular hyperplasia
26 (25)	Male	22	23	Lentiginosis, cardiac and cutaneous myxomas, neurofibromas, bilateral testicular calcification	Nodular hyperplasia

Abbreviations: CNC, Carney complex; LCCSCT, large-cell calcifying Sertoli cell tumor; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

^aReferences are cited in parentheses.

^bMother of patient 16.

Table 5
Age at Death, Sex, CNC Components, and *PRKARIA* Mutational Status of 6 Patients With Histologically Normal Thyroid Gland at Autopsy

Patient ^a	Age at Death, y	Sex	CNC Components	Cause of Death	Germline <i>PRKARIA</i> Mutation
27 (26)	35	Female	Cardiac and mammary myxoma, PPNAD	Cardiac myxoma	Not tested
28 ^b (6)	75	Female	PPNAD, lentiginos, pilonidal cyst	Pancreatic carcinoma	Absent
29 ^b (6)	44	Male	PPNAD, lentiginos, pilonidal cyst	Acute postoperative hypertension	Absent
30 (27)	14	Male	Lentiginos, cardiac and cutaneous myxomas, PPNAD	Cardiac failure (postoperative for recurrent cardiac myxoma)	Not tested
31 (28)	45	Female	Cardiac and cutaneous myxomas, PPNAD	Sudden; probable cerebral cardiac myxoma embolus	Not tested
32 (29)	54	Female	PMS, cardiac myxoma	Postoperative atrial fibrillation, respiratory insufficiency, and sepsis	Present

Abbreviations: CNC, Carney complex; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

^aReferences are in parentheses.

^bPatients 28 and 29 were fraternal twins.

Table 6
Summary of Clinical and Histopathologic Findings in the Thyroid Gland of Patients With Carney Complex

Clinical	
Normal	
Diffuse enlargement (Graves disease)	
Bilateral multinodularity	
Unilateral or bilateral mass with or without hyperthyroidism	
Large mass, suspected carcinoma	
Histopathologic	
Normal	
Benign	
Unilateral	
Adenoma, nonfunctional and “toxic,” typical and atypical	
Bilateral	
Nodular hyperplasia, micronodular diffuse and papillary hyperplasia	
Diffuse hyperplasia (presumptive) (Graves disease)	
Nodular hyperplasia	
Malignant	
Unilateral	
Carcinoma (follicular and papillary)	
Bilateral	
Carcinoma (follicular and papillary)	