

ORIGINAL ARTICLE

The Spectrum of Thyroid Gland Pathology in Carney Complex

The Importance of Follicular Carcinoma

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carney综合征

- Carney综合征（Carney complex, CNC）是一种罕见的遗传性疾病，最早于1985年由Carney et al首先描述为由粘液瘤、皮肤色素沉着、内分泌功能亢进所组成的综合征。
- PRKAR1A基因与CNC的发病有关，又称为CNC1基因。该基因位于17q22-24，编码蛋白激酶A（PKA）的调节亚基，在cAMP信号传导通路中起重要作用。PRKAR1A基因作为一种抑癌基因，其突变可能与内分泌肿瘤的发生有关。有动物实验证实该基因的突变可导致甲状腺滤泡性腺瘤及甲亢的发生。

CNC的主要特征	预计发生率(%)
原发性色素结节性肾上腺皮质增生 (PPNAD)	25-45
心脏粘液瘤	30-72
皮肤粘液瘤	63
皮肤色素沉着	62
蓝痣	
乳腺导管腺瘤	25
睾丸肿瘤	56
卵巢囊肿	67
肢端肥大症	10
甲状腺肿瘤	10
黑色素神经鞘瘤	18
骨软骨粘液瘤	<10

- 1997年，Stratakis et al 报道53位CNC患者中有3人伴有甲状腺肿瘤（1例乳头状癌，1例滤泡性癌，1例滤泡性腺瘤）；
- 2009年，Bertherat et al 报道353位CNC患者中有88人甲状腺功能紊乱，其中9人有乳头状癌和/或滤泡性癌（2.5%）；
- 本文旨在进一步研究CNC中甲状腺的临床病理特征。

材料与方法

- Mayo Clinic , J.A.C.' s files , National Institutes of Health (NIH)
- 搜集1999.1– 2016.6 间做过甲状腺手术或有甲亢表现、可能有甲状腺病变的CNC患者，并整理其临床、手术、病理和随访资料；
- 同时搜集了CNC患者中甲状腺功能正常、死于非甲状腺因素、可由尸检获得甲状腺标本的病例信息。
- 检索1999.1– 2016.6 间提及甲状腺的CNC相关文献；

- HE染色 ;
- IHC :

抗体	阳性对照	阴性对照
TG	甲状腺	睾丸、胎盘
CK19	小肠上皮	结肠和扁桃体
galectin-3	扁桃体巨噬细胞	扁桃体套区
PAX8	肾脏	肾间质
TTF-1	甲状腺	睾丸、胎盘
CT	甲状腺髓样癌	正常甲状腺
HBME-1 (mesothelial cell)	甲状腺肿瘤	正常甲状腺

结果

- 第一部分：共10例，分别来自Mayo Clinic（3例），J.A.C.'s（5例），the NIH（2例）；

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

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

*References are cited in superscript.

LCCSCT indicates large-cell calcifying Sertoli cell tumor; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

TABLE 2. Clinical Findings, Laboratory Testing Results, Preoperative and Pathologic Diagnoses, and Therapy for 10 Patients With CNC and Thyroid Tumor or Thyrotoxicosis

Patient*	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 heterogenous 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

TABLE 2. Clinical Findings, Laboratory Testing Results, Preoperative and Pathologic Diagnoses, and Therapy for 10 Patients With CNC and Thyroid Tumor or Thyrotoxicosis

Patient*	Symptoms, Clinical Findings	Ultrasonography	Fine-needle Aspiration Biopsy	Preoperative Diagnosis	Treatment	Pathologic Diagnosis
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 inhomogenous 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

*References are cited in superscript.

- 女性（8人）>男性（2人）；CNC诊断年龄9-54岁，甲状腺疾病诊断年龄12-54岁；
- 相关表现：颈部肿胀、颈部包块，Graves病典型症状、呼吸困难、甲状腺肿大或结节等；
- 病理诊断：滤泡性癌（3例），滤泡性腺瘤（3例），结节性增生（1例），弥漫性滤泡增生（2例），Hürthle细胞结节（1例）；
- 8例检测PRKAR1A突变，5例阳性，3例阴性。

- 第二部分：共6例，甲状腺临床表现正常、死于非甲状腺相关疾病、由尸检获得甲状腺组织且无异常的CNC患者

TABLE 5. Age at Death, Sex, CNC Components, and *PRKAR1A* Mutational Status of 6 Patients With Histologically Normal Thyroid Gland at Autopsy

Patient*	Age at Death (y)	Sex	CNC Components	Cause of Death	Germline <i>PRKAR1A</i> Mutation
27 ²⁶	35	Female	Cardiac and mammary myxoma, PPNAD	Cardiac myxoma	Not tested
28 ^{†6}	75	Female	PPNAD, lentigines, pilonidal cyst	Pancreatic carcinoma	Absent
29 ^{†6}	44	Male	PPNAD, lentigines, pilonidal cyst	Acute postoperative hypertension	Absent
30 ²⁷	14	Male	Lentigines, 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

*References are cited in superscript.

†Patients 28 and 29 were fraternal twins.

PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

- 第三部分，文献回顾研究，共检索CNC相关文献摘要169篇：
- 17篇（10%）显示甲状腺异常，其中15人无症状，由查体发现甲状腺病变；
- 47篇（28%）显示临床或超声检查均无异常；
- 其余105 篇（62%）未提及甲状腺。

TABLE 4. Demographic and Clinical Features and Pathologic Diagnosis of 16 Patients With CNC and Thyroid Pathologic Diagnosis

Patient*	Sex	Age at Diagnosis (y)		CNC Components	Germline <i>PRKARIA</i> Mutation	Pathologic Diagnosis
		CNC	Thyroid			
11 ¹¹	Female	64	54 and 59	PPNAD, cardiac myxoma	Not tested	Toxic adenoma at age 54 y Follicular carcinoma at age 59 y
12 ¹²	Female	53	35	Cardiac myxoma, PPNAD	Present	Follicular carcinoma
13 ¹³	Male	10	22	Cushing syndrome, PMS, LCCSCT	Present	Follicular carcinoma and follicular adenoma
14 ¹⁴	Female	19	19	Lentiginosis, cardiac and mammary myxomas	Information not available	Follicular carcinoma
15 ¹⁵	Female	31	19	Cutaneous and cardiac myxomas	Information not available	Papillary carcinoma
16 ¹⁶	Female	15	35	Cardiac and cutaneous myxomas, PMS	Present	Papillary carcinoma
17 ^{†16}	Female	45	57	Cardiac myxoma	Present	Papillary carcinoma
18 ¹⁷	Male	21	42	Cardiac myxoma, PPNAD, lentigines	Information not available	Follicular adenoma
19 ¹⁸	Female	31	31	Cardiac myxoma, PMS	Information not available	Follicular adenoma
20 ¹⁹	Female	27	27	Cardiac and mammary myxomas, Cushing syndrome	Present	Follicular adenoma
21 ²⁰	Female	20	40	Lentigines Autopsy findings: PPNAD, mammary myxoma, dilated cardiomyopathy	Present	Follicular adenoma (at autopsy)
22 ²¹	Female	13	13	Lentigines, cutaneous and cardiac myxomas, malignant PMS	Not tested	Follicular adenoma, microscopic papillary and follicular adenomatosis
23 ²²	Male	51	51	Lentigines, cardiac myxoma, pituitary adenoma (acromegaly)	Information not available	Nodular hyperplasia
24 ²³	Male	32	35	Cardiac myxoma, pituitary adenoma, LCCSCT	Present	Nodular hyperplasia
25 ²⁴	Male	46	46	Lentigines, cardiac myxoma, pituitary adenoma (acromegaly), LCCSCT	Information not available	Nodular hyperplasia
26 ²⁵	Male	22	23	Lentigines, cardiac and cutaneous myxomas, neurofibromas, bilateral testicular calcification	Information not available	Nodular hyperplasia

*References are cited in superscript.

†Mother of patient 16.

LCCSCT indicates large-cell calcifying Sertoli cell tumor; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

- 女性（10人）>男性（6人），CNC诊断年龄13-64岁，甲状腺疾病诊断年龄13-59岁；
- 多数无甲状腺相关症状，由查体发现甲状腺病变；
- 病理诊断：滤泡性癌（2例），乳头状癌（3例），滤泡性腺瘤（4例），结节性增生（4例），1人毒性腺瘤术后5年发生滤泡性癌，1人滤泡性癌伴滤泡性腺瘤，1人滤泡性腺瘤伴微小乳头状及滤泡性腺瘤病。
- 7例PRKAR1A突变阳性。

26例中共7例滤泡性癌

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

Patient*	Findings		Metastasis	Follow-up
	Gross	Microscopic		
1	Gland weighed 94 g Left lobe: Grayish-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
96,9	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

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

Patient*	Findings		Metastasis	Follow-up
	Gross	Microscopic		
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

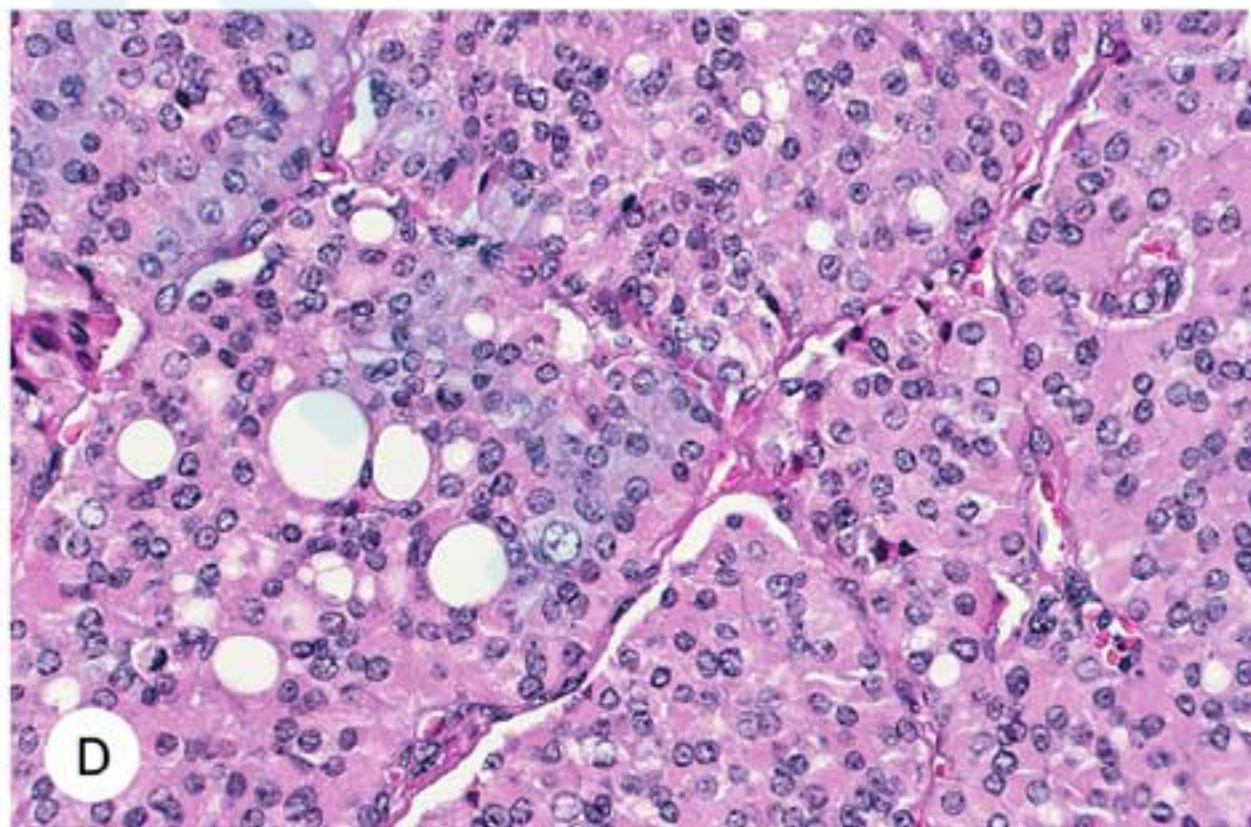
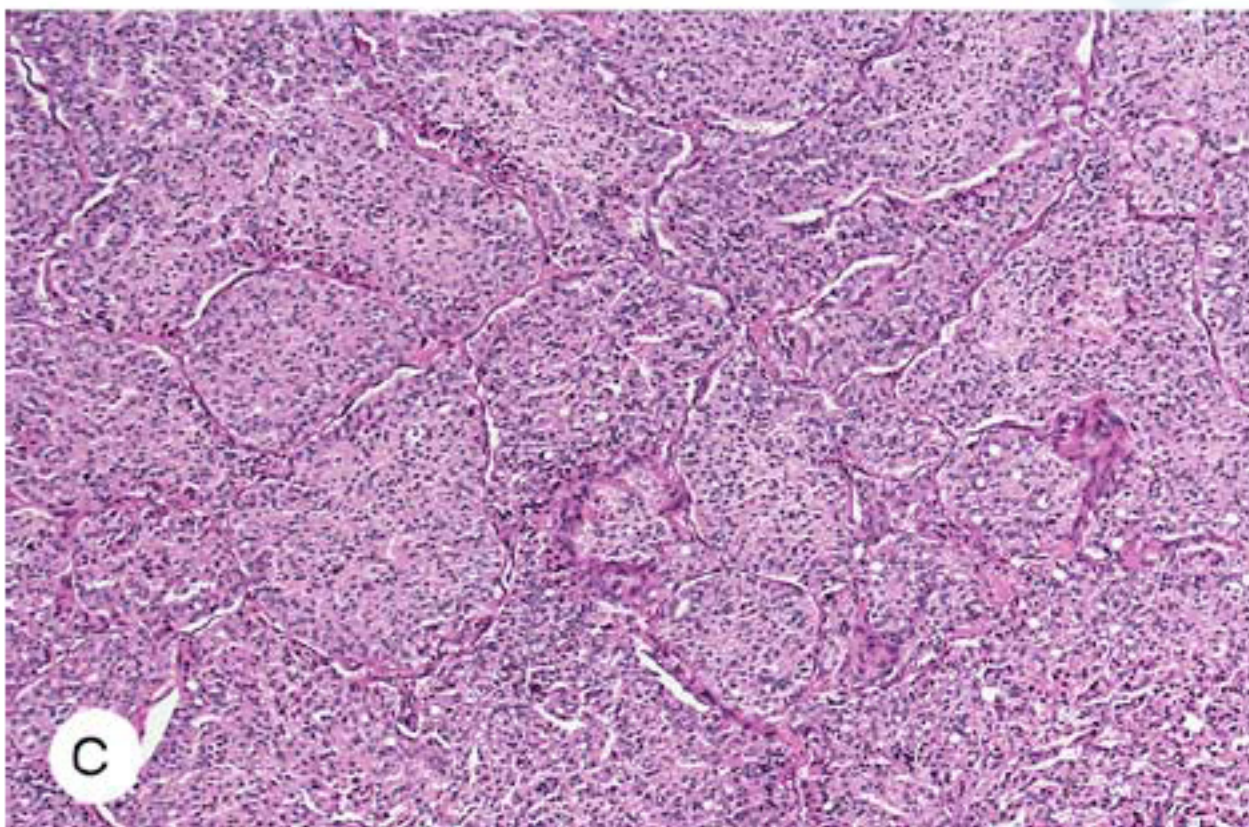
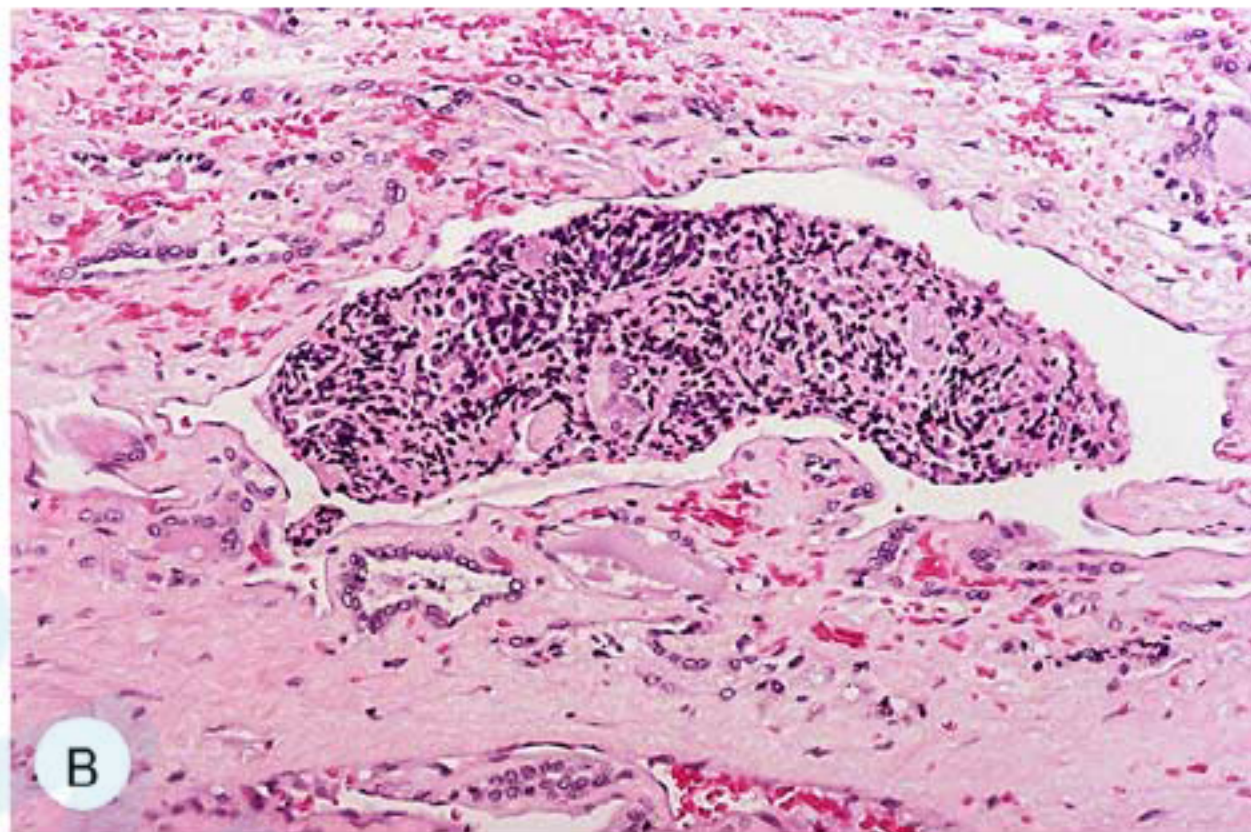
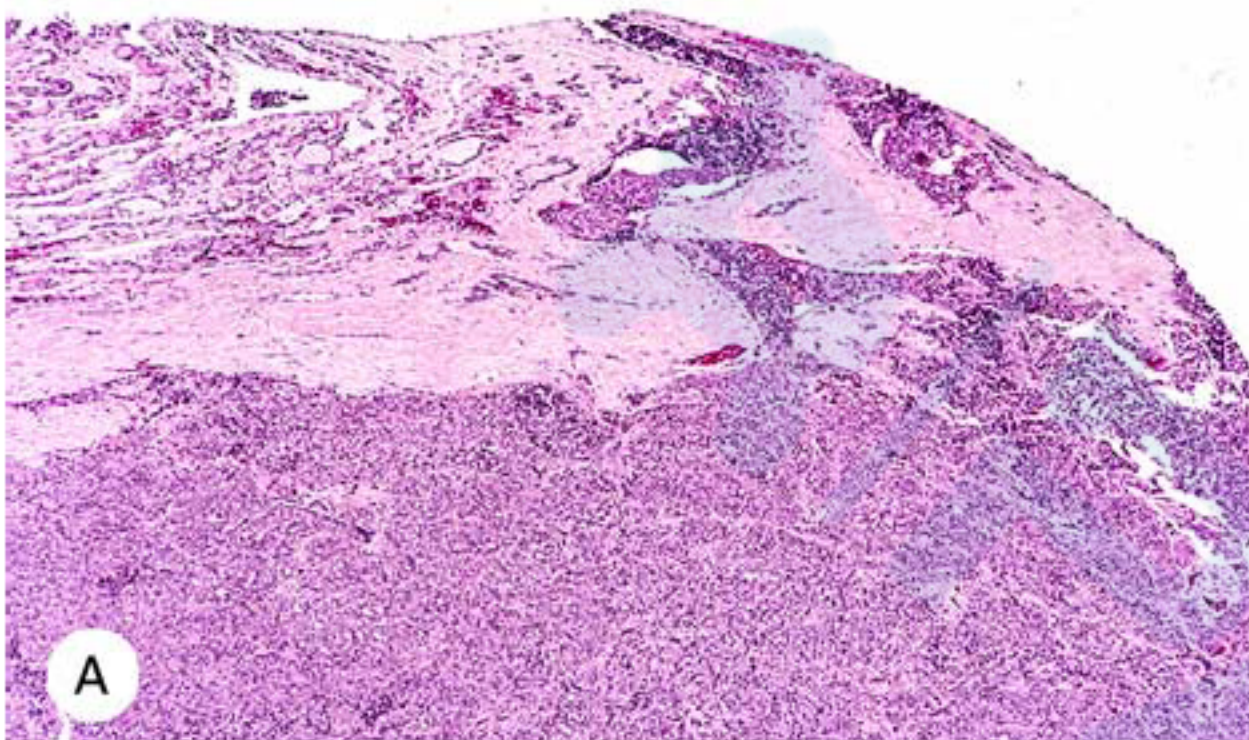
*References are cited in superscript.

- 大体表现：甲状腺结节，直径0.5-6.5cm，其中4例直径 $\geq 3\text{cm}$ ；
- 镜下：瘤细胞立方形或多角形，多为嗜酸性胞浆，排列成小梁状、索状、滤泡状、巢状或实性，中等异型性，可见包膜及血管侵犯；
- 3例发生淋巴结和/或肺转移，并死亡。

第一部分3例滤泡性癌：

- TG胞浆阳性 (3/3) ,
- PAX8核阳性 (3/3) ,
- 50%肿瘤细胞HBME-1核阳性(2/3) ,
- galectin-3 散在阳性(3/3) ,
- CK19和CT阴性(3/3)。

Follicular carcinoma (patient 9)



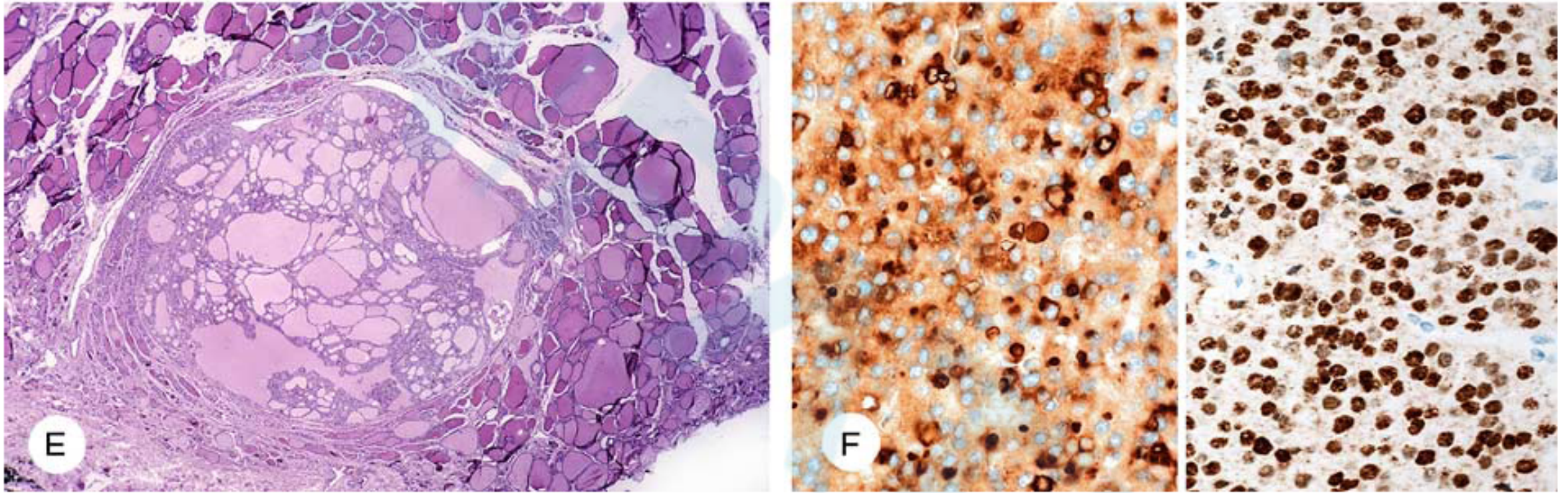


FIGURE 1. Follicular carcinoma (patient 9). A, Solid tumor with a thick, fibrous capsule invaded by tumor. B, Capsular intravascular tumor thrombus. C, Tumor cells arranged in a coarse alveolar and trabecular pattern. D, Sheet of relatively small cells with eosinophilic cytoplasm and regular hyperchromatic 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).

- 第22例：
- 13岁女童，因无症状的结节性甲状腺肿行甲状腺全切术，
- 可见1.5×1×1cm肿瘤，病理诊断为“multifocal papillary and follicular hyperplasia, atypical.”
- 作者认为结节性甲状腺肿，伴滤泡性腺瘤及微小滤泡性腺瘤病。

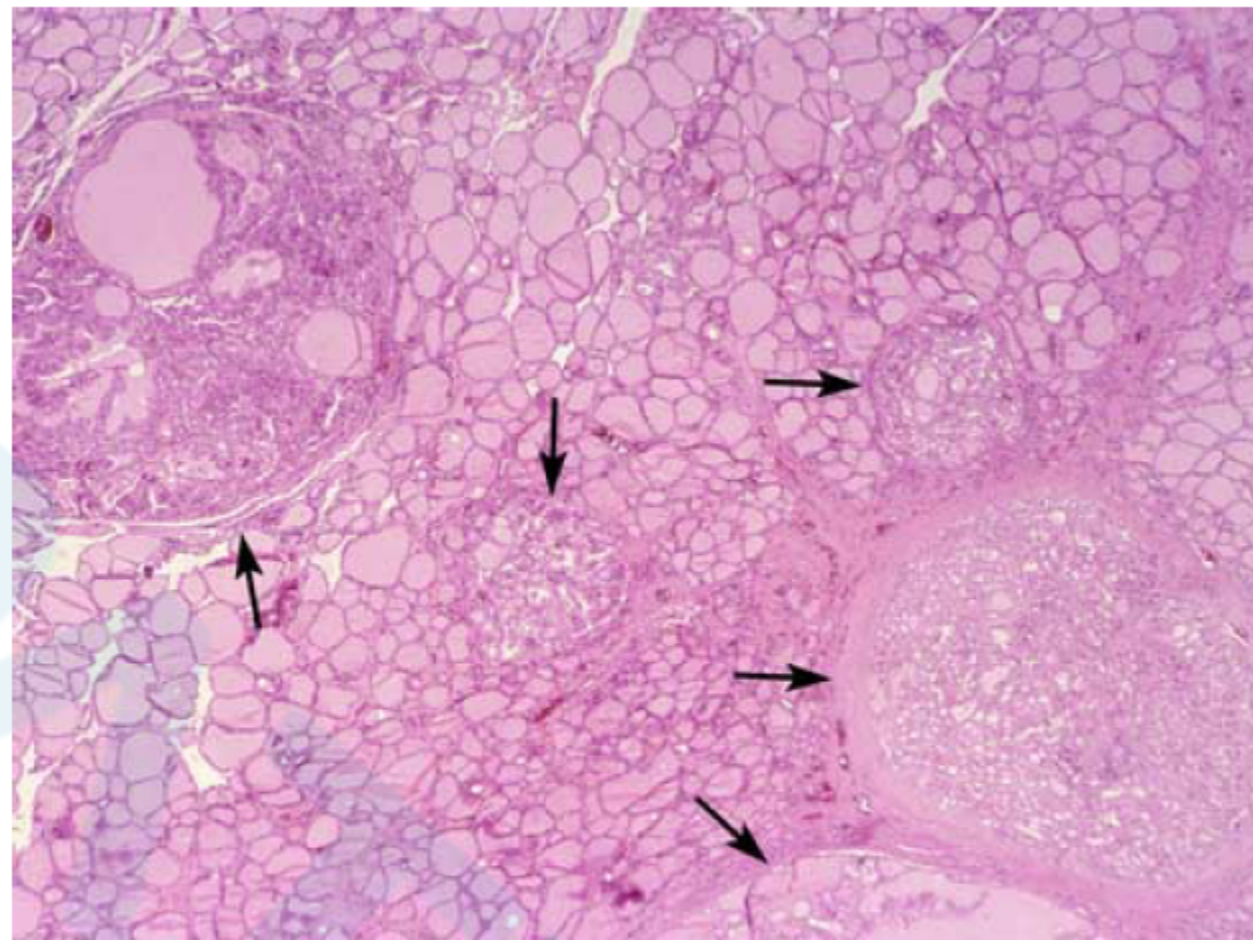


FIGURE 2. Follicular adenomatosis (patient 22). Low-power image of extratumoral thyroid showed multiple capsulated and unencapsulated microfollicular and macrofollicular lesions (arrows) in normal colloid thyroid.

讨论

- 本文共整理了26例CNC甲状腺病变；
- 10例来自Mayo Clinic、J.A.C.'s、the NIH，16例来自文献检索；
- 部分患者有甲状腺相关症状；而多数无症状，由查体发现甲状腺异常；
- 多为女性，男女比例大约1:2；
- 甲状腺疾病诊断年龄12-64岁，中位年龄34岁；

- 甲状腺病理诊断主要包括：滤泡性癌、乳头状癌、滤泡性腺瘤、结节性增生；
- 滤泡性癌是CNC中最严重的甲状腺疾病，多为中年人，4例肿瘤直径大于3cm，2例为多灶性；3例淋巴结和/或肺转移并死亡。转移灶对碘131和乐伐替尼不敏感。
- CNC患者滤泡性癌的发生率多于乳头状癌，与普通人群的发病率相反。

TABLE 6. Summary of Clinical and Histopathologic Findings in the Thyroid Gland of Patients With CNC

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)

结论

- CNC中甲状腺病变可以是毒性的或无功能的，可以是增生性病变或肿瘤性病变，可以是良性的或恶性的，应将甲亢列入CNC临床特征，将滤泡性增生纳入CNC甲状腺病变谱系；
- 滤泡性癌是CNC中最严重的甲状腺疾病，多见于中年女性，且易发生转移，预后差；
- 对CNC患者应长期随访，每年进行甲状腺超声检查，以利于甲状腺疾病的早发现和早治疗。

*Thank
You!*

