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Authors
Nwokoro, NA
Korytkowski, MT
Rose, S
et al.

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Spectrum of Malignancy and Premalignancy in Carney Syndrome

Ngozi A. Nwokoro,[1,2]* Mary T. Korytkowski,[3] Suzanne Rose,[3] Michael B. Gorin,[4] Mona Penles Stadler,[2] Selma F. Witchel,[5] and John J. Mulvihill[2]

[1]*Department of Oral and Maxillofacial Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania*
[2]*Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania*
[3]*Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania*
[4]*Department of Ophthalmology, University of Pittsburgh, Pittsburgh, Pennsylvania*
[5]*Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania*

Carney syndrome is a rare, autosomal dominant, multi-system disorder comprising 8 well-characterized findings, only 2 of which need be present for a definitive diagnosis. Benign neoplasms are frequent, but malignancies are thought to be uncommon. We have studied a family to clarify the diagnosis and spectrum of clinical manifestations of the syndrome and to develop guidelines for management. The proposita, a 34-year-old woman had classic findings of Carney syndrome, invasive follicular carcinoma of the thyroid gland, Barrett metaplasia of the esophagus, neoplastic colonic polyps, bipolar affective disorder, and atypical mesenchymal neoplasm of the uterine cervix distinct from the myxoid uterine leiomyoma usually seen in this syndrome. Although thyroid gland neoplasm is rare in Carney syndrome, this patient's most aggressive manifestation was her thyroid carcinoma. The diagnosis of Carney syndrome was established in her 9-year-old son and is a probable diagnosis in her 12-year-old daughter. Endocrine manifestations were prominent in the family with at least 9 relatives in 3 generations affected with various endocrine abnormalities. The findings in this family indicate that the spectrum of manifestations in this pleiotropic gene apparently includes a malignant course with premalignant and endocrinologic disorders not previously recognized. Am. J. Med. Genet. 73:369–377, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Carney syndrome; cardiac myxoma; Barrett metaplasia; neoplastic colonic polyps; subcapsular cataracts; follicular thyroid carcinoma

INTRODUCTION

Carney syndrome (MIM number 160980) is a rare, multi-system, pre-neoplastic syndrome diagnosed when at least 2 of the following 8 findings are present: cardiac myxoma, cutaneous myxoma, myxoid mammary fibroadenoma, spotty mucocutaneous pigmentation including lentigines and blue nevi, primary pigmented nodular adrenocortical disease (Cushing syndrome), testicular tumor, growth-hormone–secreting pituitary adenoma, and psammomatous melanotic schwannoma [Carney et al., 1985, 1986a,b; Cook et al., 1987; Kennedy et al., 1987; Carney, 1990]. Based on at least 56 certain cases, the mode of inheritance appears to be autosomal dominant [Kennedy et al., 1991; Koopman and Happle, 1991[.

Malignant neoplasms are infrequently seen in this disorder. Our 34-year-old proposita with Carney syndrome had atypical malignant and premalignant neoplasms as did variously affected relatives. Taken together, these findings expand our knowledge of the syndrome.

CLINICAL REPORTS

Detailed studies of the proposita and her 2 children (half sibs, Fig. 1) were conducted, including review of medical records and multi-disciplinary clinical and laboratory evaluations. Family history and records of other relatives were also reviewed, but these individuals were not personally examined.

The Proposita

Individual III-6 (Fig. 2) presented at age 31 years because of an unusual multi-system syndrome. Now age 34 years, she is a gravida 4, para 2, aborta 2 woman with a history of multiple nevi, diffuse facial lentigines, and labial pigmentation, all apparent at an early age.

*Correspondence to: Ngozi A. Nwokoro, Ph.D., M.D., Department of Human Genetics, Graduate School of Public Health, A300 Crabtree Hall, 130 DeSoto Street, Pittsburgh, PA 15261.

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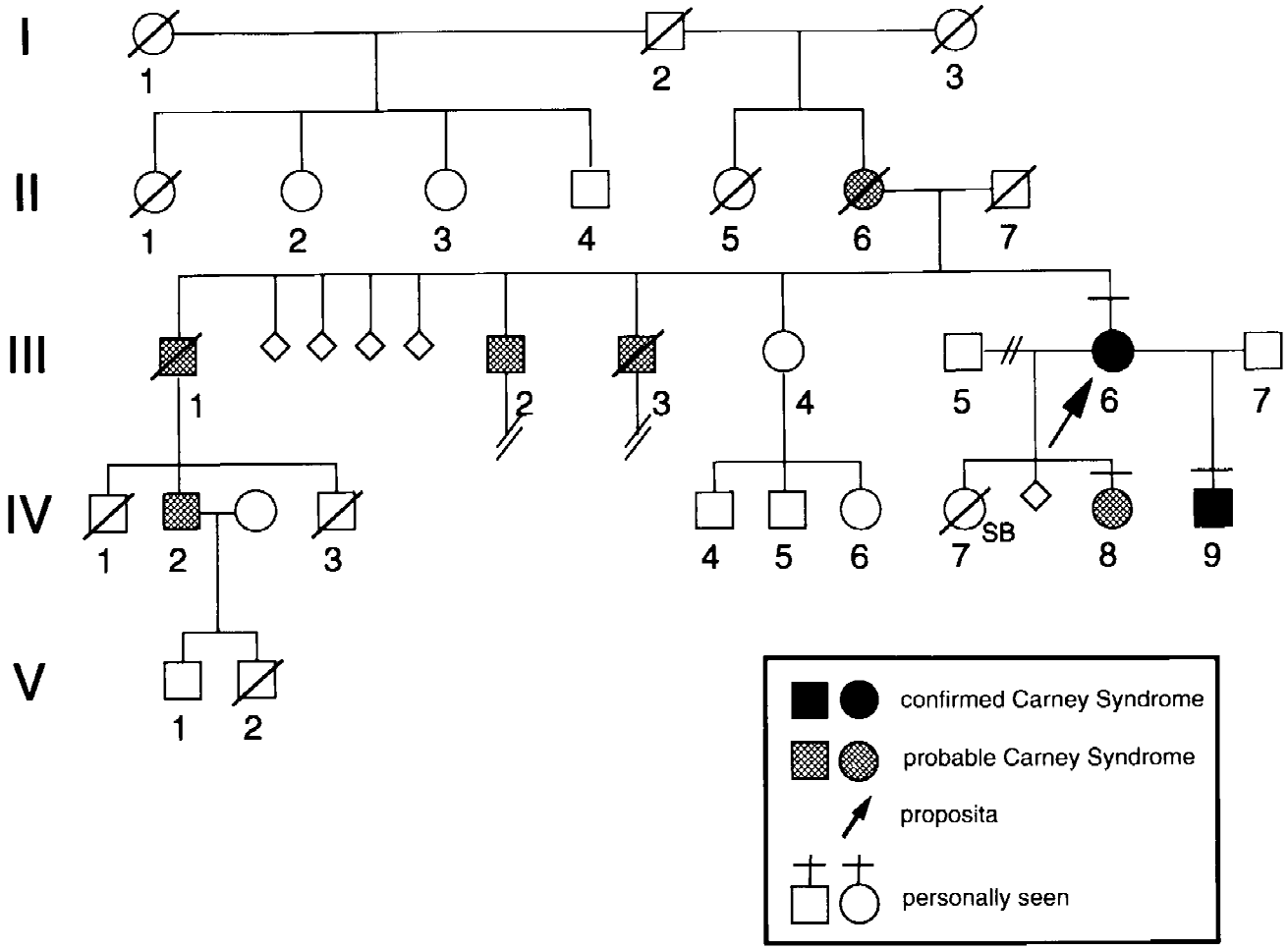

Fig. 1. Pedigree. Symbols.

At birth she had a large, multi-pigmented hairy patch across her left lower abdomen and, by age 2 years, had developed several pigmented skin lesions and masses. Since the age of 2 years, she had multiple removals of cutaneous tumors, a hemangioma of the right lower eyelid, a peripheral myxoid tumor of the right lower eyelid, fibromyxomatous lesions from the right axilla, and papillomas of the right nipple and right labia. Excised lesions from her checks included an angiofibroma, a myxoma, cavernous hemangiomas, and a sebaceous adenoma. Results of punch biopsies showed myxofibroma and papilloma of the right occipital region, keloid of the right ear lobe, focal dermal mucinosis of the back and the right nipple, focal dermal mucinosis or myxoma of the right buttock, and labial lentigo. Hirsutism of face, trunk, and limbs, was first noted at age 10 years, required frequent shaving as a teenager, worsened by age 27 years, and continues to be a major cosmetic problem. Dermatological evaluation at 30 years led to a diagnosis of LAMB syndrome [Rhodes et al., 1984]. Skin biopsy results prompted an evaluation for the presence of cardiac myomas by echocardiography. This showed right ventricular tumors that were thought to account for the several years' history of easy fatiguability, increasing dyspnea, and severe palpitations. At surgery, 4 distinct right ventricular myxomas (1.8 × 1.5 × 1.1, 0.7 × 0.4 × 0.4, 0.6 × 0.6 × 0.5, and 1.4 × 0.9 × 0.8 cm) were found and resected. Cardiac symptoms resolved, and no additional masses have been seen on yearly echocardiographic evaluations.

Before the diagnosis of LAMB syndrome at age 30 years, she presented to the endocrine clinic for further evaluation of a thyroid nodule involving the lower pole of the right lobe. Results of thyroid function studies were normal. Fine-needle aspiration biopsy of the nodule was performed on 2 occasions 6 months apart. The first was performed at an outside hospital and was reported as benign. A second, reported as adequate for interpretation, showed clumps of atypical—probably benign—follicular epithelial cells. The continued growth of the nodule despite measured thyrotropin (TSH) levels of 0.3–0.5 IU/ml (normal = 0.5–5 IU/ml) prompted surgical excision of the nodule in July 1992. A frozen section demonstrated follicular carcinoma, and a total thyroidectomy was performed. Histopathological examination showed a 3.0 cm follicular thyroid carcinoma with angiolymphatic invasion and extensive parenchymal infiltration with a separate adjacent 0.5 cm encapsulated follicular carcinoma in the right lobe.

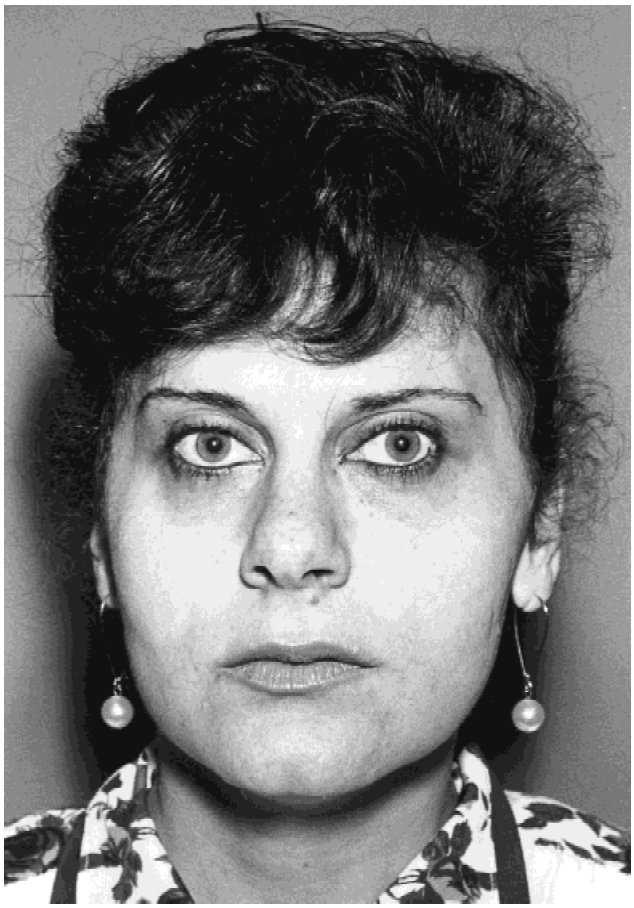

Fig. 2. The proposita at age 32 years.

There was also a 0.5 cm follicular adenoma in the left lobe. Because of the size and aggressiveness of the thyroid neoplasm, 150 mCi of ^{131}I was administered in August 1992 to ablate any remaining thyroid tissue. Although there was a lack of uptake on a pre-treatment ^{131}I, a second dose of 150 mCi was given in March 1993 because of an elevated thyroglobulin level of 325 ng/ml (normal = 5–50 ng/ml). A post-treatment scan demonstrated an area of focal increased uptake in the neck slightly to the right of the midline. Despite continued suppressive therapy with L-thyroxine to maintain the TSH level at <0.03 IU/ml, the elevation in serum thyroglobulin persisted. A recent sonogram of the neck demonstrated three solid masses in the anterior neck, a finding confirmed by computed tomography (CT) scan. These lesions were excised, and the histopathological findings were those of aggressive follicular carcinoma.

The additional clinical findings of weight gain, borderline vascular hypertension (136/86 mm Hg), hirsutism (Ferriman and Gallway [1961] score = 13), and a history of depression led to an evaluation for Cushing syndrome. There were no clinical signs of acromegaly. A 24-hour urine free cortisol (UFC) level was elevated at 166 μg/day (normal = 20–90 μg/day). A morning plasma cortisol did not suppress with a low-dose overnight dexamethasone suppression test (DST, 8 AM cortisol = 8 μg/dl). Following a 2-day low-dose (2.0 mg/day) DST, suboptimal suppression of UFC was observed (UFC = 52 μg/day) with normal suppression of 17-hydroxycorticosteroids. An overnight high-dose DST (8 mg at night) was associated with a paradoxical rise in plasma cortisol. A repeat 24-hour UFC 6 months later was normal at 84 μg/day. An abdominal CT scan showed bilateral nodular adrenal enlargement, a finding well documented in Carney syndrome [Carney and Young, 1992]. Although repeat UFC remained normal, there were low plasma levels of dehydroepiandrosterone (DHEA, 18 ng/dl; normal = 130–980 ng/dl) and dehydroepiandrosterone sulfate (DHEA-S, <5 μg/dl; normal = 50–542 μg/dl), suggesting autonomously functioning adrenals [Braithwaite et al., 1989].

As part of an evaluation for hirsutism, plasma growth hormone (GH) and somatomedian-C (SM-C, IGF-1) were measured in addition to circulating androgens. Despite the absence of clinical findings of acromegaly, the patient's SM-C level was elevated at 616 ng/ml (normal = 114–492 ng/ml), with a normal GH of 2.7 ng/ml. Abnormal GH secretion was further verified during a 3-hour oral glucose tolerance test in which a basal GH level of 8.5 ng/ml failed to suppress to <2 mg/ml. Measurement of growth-hormone–releasing hormone was normal (39 pg/ml). Magnetic resonance imaging (MRI) of the pituitary was normal. These endocrine findings are shown in Table I.

Gastrointestinal findings included chronic cholecystitis and cholelithiasis, erosive esophagitis, gastritis, duodenitis, duodenal ulcer, colitis, and colonic polyps. The endoscopic impression of Barrett metaplasia, i.e.,

TABLE I. Results of Studies of Pituitary-Adrenal Function in the Proposita*

	ACTH (pg/ml)	UFC (μg/day)	17-OHCS (mg/d)	Cortisol (μg/dl)
Adrenal testing	18	134	15	8
Baseline				
Dexamethasone (2 mg/d) Day 2		52	1.3	12
Dexamethasone (8 mg at 11 PM) Day 3				16

Pituitary Testing	0 min	30 min	60 min	120 min	180 min
OGTT					
Glucose (mg/dl)	89	133	92	64	75
GH (ng/ml)	8.9		6.1	5.0	7.5
L-DOPA (500 mg PO)					
GH (ng/ml)	6.0	3.3	14.7	3.8	

	Baseline	30 days (ng/dl)
Octreotide		
GH	5.3	4.9
SM-C	695	524

	(1991)	(1993)
Androgens		
LH/FSH (mlU/ml)	2.3/2.0	
17-OHP (ng/dl)	92	
Total T (ng/dl)		19
Free T (pg/ml)	2.0	4.4
(%)	1.07	2.29
Prolactin (ng/ml)	7.2	

*ACTH, corticotropin; UFC, urinary free cortisol; 17-OHCS, 17-hydroxycorticosteroids; OGTT, oral glucose tolerance test; GH, growth hormone; SM-C, somatomedin-C; LH, luteinizing hormone; FSH, follicle-stimulating hormone; 17-OHP, 17-hyrdroxyprogesterone; T, testosterone.

erythematous tongues of tissue extending 3.5 cm above the gastroesophageal junction (Fig. 3), was confirmed by histopathological studies of biopsy specimens. A 1.5 × 1.5 × 1.0 cm tubulovillous adenoma was removed from the sigmoid colon at 25 cm, and a 4-mm polyp in the transverse colon showed mild superficial epithelial hyperplasia. The colonic mucosa appeared hypervascular, with biopsy specimens of the cecum revealing chronic inflammation. On subsequent colonoscopic evaluation, a rectal biopsy specimen of an area of granularity and erythema showed a moderate lymphocytic (plasma cell) infiltrate with capillary vascular congestion within the lamina propria.

At age 32 years, the patient presented to the gynecology clinic after 6 months of vaginal bleeding and abdominal pain. Ultrasonography showed a 3.0 × 3.5 × 3.5 cm round pelvic mass with mixed echogenicity that was posterior to the cervix. Total abdominal hysterectomy was performed, and the histopathology of the lesion was that of an atypical mesenchymal cervical neoplasm of indeterminate malignant potential. Following several years' history of painful tender breast nodules, the patient also had needle biopsy of three of the largest nodules; the pathological findings indicated fibroadenoma.

Her history also recorded excision of a fibromyxomatous lesion from the right distal humerus at age 4 years, bipolar affective disorder first noted during the patient's adolescent years, recurrent headaches, slowly progressive left sensori-neural hearing deficit of childhood onset, dry eyes and mouth, persistent left submandibular lymphadenopathy, episodic galactorrhea, arthralgias, chronic lower back pain, chronic mild peripheral edema, and chronic fatigue. Cranial CT scan with enhancement and MRI of the brain were normal. Chromosomes of peripheral blood lymphocytes were normal.

Examination of the proposita (Fig. 2) showed her to be a normal-appearing woman with generalized freckling and spotty pigmentation of trunk and breasts. She

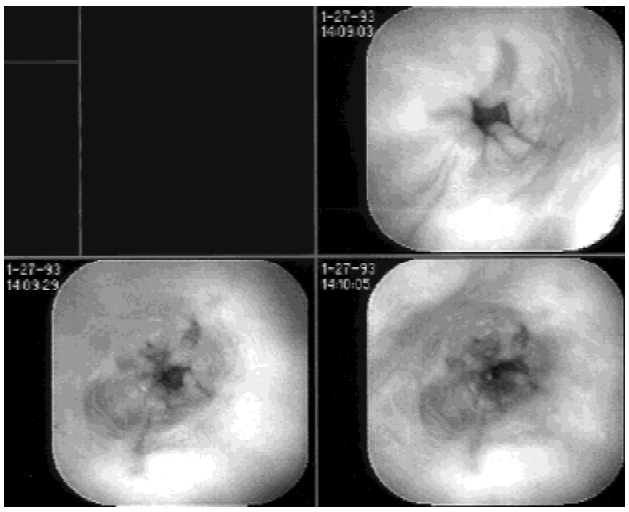

Fig. 3. Endoscopy photographs of the esophagus showing erythematous tongues of tissue extending proximally from the gastroesophageal junction consistent with Barrett metaplasia.

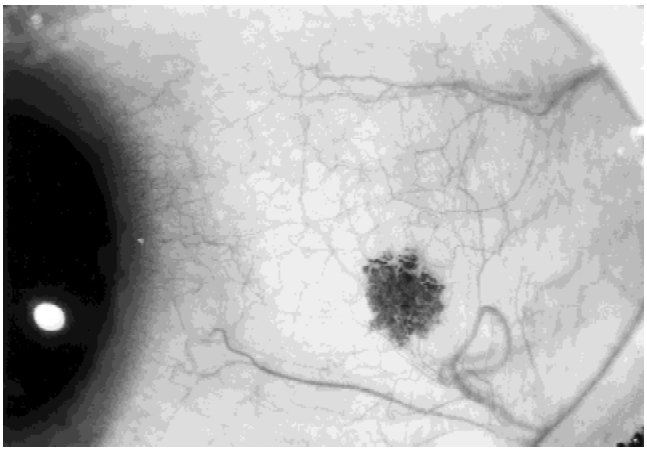

Fig. 4. Conjunctival nevus of the left eye.

had lentigines and freckles on the face and eyelids, conjunctival nevus and pigmented caruncle in the left eye (Fig. 4,5), and bilateral posterior subcapsular cataracts (Fig. 6). She also had pigmented macules of the right lower lip and vermilion borders, four pigmented macules on the left buccal mucosa, cutaneous and subcutaneous myxoid nodules mostly of the face and trunk, and multiple macular blue nevi of the labia majora, labia minora, and anal canal. Other findings included left submandibular lymphadenopathy, multiple breast nodules, a large multi-pigmented ellipsoid hairy lesion (15 cm diameter) on the left lower quadrant of her abdomen, and hirsutism involving face, inframammary region, lower abdomen, and limbs (Fig. 7). The rest of her findings were consistent with history.

Relatives (Fig. 1, Table II)

The daughter, IV-8, was born in 1979. Findings from a recent examination included macrocephaly (>98th centile), facial and truncal freckles, two café-au-lait macules on the back and left thigh, multiple thoracic and upper arm nevi, and two pigmented macules on the surface of her right labium majus. Facial and truncal hirsutism was initially noted when she was 9 years old, and this has now extended to her lower abdomen, buttocks, and limbs. Her menses are regular, and her pubertal development was Tanner stage 5 for breast and pubic hair development. Two determinations of her UFC excretions were 21.2 and 45.4 μg/day (normal = 20–100 μg/day). Plasma testosterone was elevated at 132 ng/dl (normal = <70 ng/dl for adult women). ACTH stimulation test was consistent but not diagnostic of decreased 3β-hydroxysteroid dehydrogenease activity, with 17-hydroxypregnenolone incremental elevation of 2,183 ng/dl (99% confidence interval for incremental elevation = 1,263 ng/dl), DHEA incremental elevation of 1,428 ng/dl (99% confidence interval = 1,109 ng/dl), and 17-hydroxypregnenolone/17-hydroxyprogesterone ratio at 30 minutes of 9.6 (99% confidence interval = 10) [Siegel et al., 1990]. She had normal growth hormone levels. Abdominal and pelvic ultrasonography showed a normal uterus, normal ovaries with small follicular

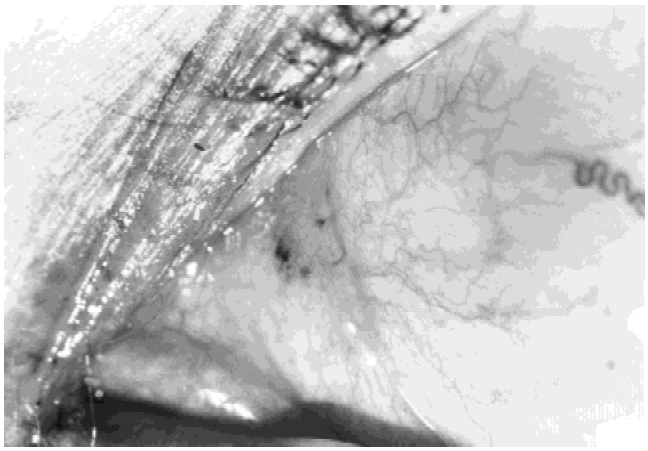

Fig. 5. Pigmented nevi of the left caruncle.

cysts, and no adrenal mass lesions. Recent MRI of her adrenal glands was within normal limits. Echocardiography has been normal.

The diagnosis of Carney syndrome was made in the son (IV-9) during the initial genetic evaluation. Born in 1984, he had macrocephaly (>98th centile), generalized hirsutism, multiple freckles, facial lentigines (especially around both eyes), two small nevi on the right lower lid, and pigmentation of the left caruncle. Fundoscopic examination showed a small cluster of three atypical hyperpigmented nevi seen at 9:30 near the equator in the right eye (Fig. 8). These nevi appeared to arise from the pigment epithelium rather than from the choroid and bore a close resemblance to congenital hypertrophy of the pigment epithelium or "bear tracts." Other findings included multiple cutaneous lesions; spotty pigmented lesions of the ears, buccal mucosa, neck, trunk, arms, and popliteal fossa; café-au-lait spots of the right neck; pigmented nevi of the upper chest and arms, right upper arm, and right popliteal fossa; three facial myxomas (two verified by histopathological studies of biopsy specimens); a right forehead myxoma and associated epidermoid cyst; bilateral upper anterior chest myxomas; and a subcutaneous cystic lesion in the right upper quadrant of the abdomen. Myxomatous lesions were excised from the right clavicle, left axilla, and right upper quadrant of the abdomen. Pubic hair and genital development were prepubertal, but testes were hard and enlarged with the left larger than the right. Testicular ultrasonography showed bilateral calcified lesions with extensive involvement of the left testis. At left orchiectomy, the upper portion of the testis appeared normal, whereas the lower portion was "rock hard." Histological examination of the lesion showed a calcifying Sertoli cell tumor characterized by multi-focal sheets and cords of cells with abundant acidophilic cytoplasm and large areas of amorphous calcification. Gonadotropin-releasing hormone stimulation test showed peak luteinizing hormone of 1.36 U/L, peak follicle stimulating hormone of 1.2 U/L, and plasma testosterone <10 ng/dl, findings consistent with the prepubertal status noted on physical examination. A random growth hormone level was 3.7 ng/dl. UFC excretion was 25.4 μg/dl. Echocardiogram was normal.

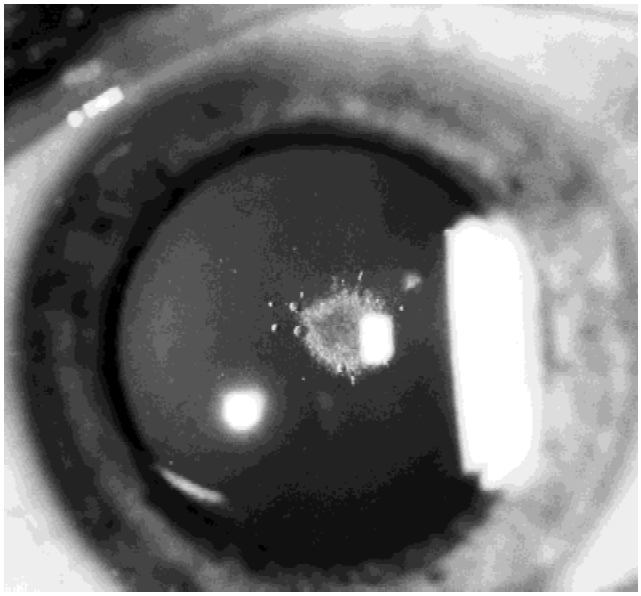

Fig. 6. Posterior subcapsular cataract of the left eye as demonstrated by retroillumination.

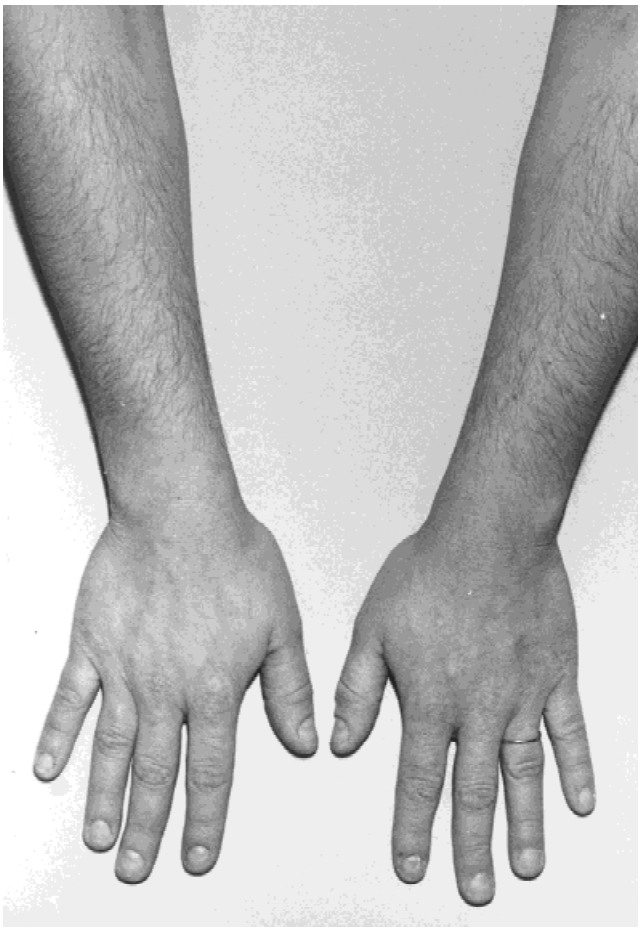

Fig. 7. Upper limbs of proposita showing extensive hirsutism despite regular shaving.

TABLE II. Clinical Manifestations in Relatives*

						Brothers			Nephews	
	Proposita (III-6)	Daughter (IV-8)	Son (IV-9)	Mother (II-6)	Sister (III-4)	1 (III-1)	2 (III-2)	3 (III-3)	1 (IV-1)	2 (IV-2)
Age at follow-up or (death) (yr)	34	12	8	(62)	43	(50)	49	(39)	(5)	28
Manifestations										
Skin										
Cutaneous or subcutaneous nodules	+	−	+	+						
Lentigines and freckles	+	+	+	+			+	+		
Café-au-lait spots (<6)	+	+	+							
Dermal mucinosis	+	+	+							
Eyelid lesions	+	−	+	+			+			
Hirsutism	+	+	+	+	+	+	+	+		+
Endocrine										
Hyper- or hypothyroidism	+	−	−	−	−	+	+	−	−	+
Hyperparathyroidism	−	−	−	+						
Hypopituitarism	−	−	−	−	−	−	−	−	−	+
Pituitary microadenoma								+		
Calcifying testicular tumor	na	na	+	na	na					
Other										
Lip and buccal pigmentation	+	+	+							
Malignant neoplasia	+	−	+	−	−	−		+		
Labial lesions	+	+	na			na	na	na	na	na
Multiple breast nodules	+	−	na		+	na	na	na	na	na
Intraosseous myxoma	+	−	+					+		
Neuromuscular disease	−	−	−		−	−	−	+		
Affective disorder or schizophrenia	+	−	−	+	+			+		

*+, present; −, absent; na, not applicable; blank, not known.

The maternal family history strongly suggested a diagnosis of Carney syndrome in 5 other relatives (Fig. 1, Table II). There are many heavily freckled individuals and all presumably affected relatives had thyroid abnormalities, except II-6, who had hyperparathyroidism. The three members of generation II with hyperthyroidism had only limited available historical information, but II-1 had carcinoma of the thyroid. Individual II-6 had generalized freckling, pigmented nevi of the eyelids, spotty pigmentation of trunk and limbs, multiple subcutaneous nodules, and borderline diabetes mellitus. She died suddenly at age 62 years, and an autopsy was not performed.

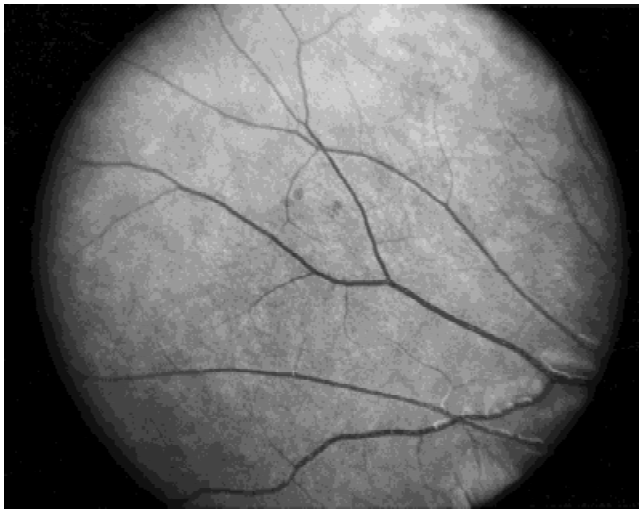

Fig. 8. The superonasal portion of the fundus of the right eye of the proposita's son. The small cluster of three lesions represents focal hyperpigmentation of the retinal pigment epithelium as distinguished from nevi of the choroid. No other retinal, retinal pigment epithelium, or choroidal abnormalities were noted in either eye.

III-1's history is very consistent with hyperthyroidism, and his sudden death at age 50 years was attributed to malignant hypertension; there was no autopsy. He had 3 sons, all of whom had complex congenital heart disease. The eldest (IV-1) had ventricular septal defect (VSD), pulmonic valve stenosis, aortic insufficiency, and mild infundibular stenosis. He died at 5 years from complications of his congenital heart disease despite early surgical correction. Autopsy showed 2 accessory spleens, right double pelvises and ureters, and Meckel diverticulum. Individual IV-2 had tetralogy of Fallot, myxedema, and hypopituitarism as a child and recently presented with hyperthyroidism that is being investigated. He has a left visual field defect of unknown cause, is learning-disabled, and has a history of cardiac arrhythmias. One of his sons has congenital hearing loss and is developmentally delayed. Relative IV-3 had transposition of the great arteries, VSD, and learning disabilities associated with behavior problems. He died at age 19 years of complications from his congenital heart disease.

III-2, a 49-year-old man, had generalized freckling, subcutaneous nodules, eyelid skin tags, infertility of unknown cause, subcutaneous abdominal masses managed by repeat surgical excisions, hyperthyroidism, thyrotoxicosis, and partial thyroidectomy, the histopathologic report of which was unavailable. His brother, III-3, had generalized freckling and spotty pigmentation of trunk and limbs and was mildly mentally retarded. He was institutionalized at age 22 years with the diagnosis of paranoid schizophrenia and an unspecified neuromuscular defect (a maternal aunt, II-5, who died at age 62 years, also had an unspecified "musculardystrophy"). Spinal MRI showed congenital spinal stenosis from C3 to C6, a large focal herniation at C4-C5 compressing the spinal cord (a finding confirmed by myelography), and a smaller focal herniation to the

mid-line at C6-C7 that deformed the cord at this level. He died at age 39 years from bowel obstruction due to colon cancer. Autopsy findings included metastatic adenocarcinoma of the sigmoid colon, an undifferentiated chromophobic microadenoma of the pituitary gland, ulcerative esophagitis, ulcerative colitis, bifid left ureter, hemosiderosis of the liver, and cardiac findings consistent with previous rheumatic heart disease. Relative III-4 had hirsutism, large hands and feet, clinical fibrocystic breast disease, symptomatic uterine fibroids that resulted in hysterectomy at age 30 years, and bipolar affective disorder managed by lithium. A son and a daughter were heavily freckled, but with no other contributory findings of note.

DISCUSSION

The Carney syndrome was initially called the NAME syndrome (nevi, atrial myxoma, mucocutaneous myxomas, ephelides) [Atherton et al., 1980] and later the LAMB syndrome (lentigines, atrial myxomas, mucocutaneous myxomas, blue nevi) [Rhodes et al., 1984]. Neither acronym adequately describes this multi-system disorder [Carney et al., 1985]. Although some lesions are congenital or of childhood onset, the diagnosis is usually not made until in the second and third decades of life (average age 24 years). More than 80% of patients either have pigmented skin lesions (lentigines, compound nevi, or blue nevi) or cutaneous myxomas. The most common site for the cutaneous myxomas is the eyelid. Other ophthalmic findings include spotty pigmentation of the eyelids and pigmented lesions of the caruncles [Carney et al., 1985; Kennedy et al., 1987, 1991]. The proposita in this study had bilateral posterior subcapsular cataracts. To our knowledge, cataracts have not been described previously in Carney syndrome. The three small, unusual pigmented epithelial nevi seen in her son may also be associated with this syndrome. However, pigmented epithelial nevi are not uncommon in the general population.

The heart is the next most frequently affected organ. Among 40 patients, 72% had 1 or more cardiac myoxomas, most of which were atrial myxomas [Carney et al., 1985]. The myxomas can cause refractory congestive heart failure. Embolization from cardiac myxomas is the usual cause of early death, hence the importance of periodic echocardiographic surveillance. Myxoid fibroadenomas of the breast are also common. Other tumors include schwannoma in 3 patients and microscopic pheochromocytoma [Vidaillet et al., 1987], acoustic neuroma [Mansell et al., 1991], benign ovarian cystic teratoma, ovarian cyst, and encapsulated follicular carcinoma of the thyroid [Carney et al., 1985; Vidaillet et al., 1987] in one patient each. Since tumors associated with the Carney syndrome tend to be benign, conservative treatment has usually been recommended [Carney et al., 1985].

Endocrine involvement is a common manifestation in Carney syndrome, with the adrenal glands being the most frequently affected [Carney and Young, 1992]. Testicular tumors occur in half of the affected males. The pituitary gland is involved in 10% of all cases. Thyroid involvement is infrequent. The most common endocrine manifestation of Carney syndrome is primary pigmented nodular adrenal hyperplasia (PPNAH), affecting 40% of individuals [Carney et al., 1985; Cheung and Thompson, 1988; Gaillard et al., 1988; Young et al., 1989; Kennedy et al., 1991]. Cushing syndrome is the presenting condition in 20% of cases and occurs at a young age (range 4–19 years). A paradoxical increase in urinary and plasma cortisol levels following DST has been observed in such patients [Young et al., 1989]. ACTH levels have been normal, low, or undetectable [Braithwaite et al., 1989; Young et al., 1989; Carney and Young, 1992]. Our patient had episodic hypercortisolism, low DHEA, low DHEA-S, and unresponsiveness to dexamethasone suppression, findings consistent with autonomously functioning adrenal glands [Carney and Young, 1992]. However, an ACTH level was within the normal range at 18 pg/ml. One explanation for this normal ACTH level is that the patient's pituitary gland is usually exposed to normal levels of circulating cortisol.

Adrenal stimulating immunoglobulins (ASI), acting as ACTH-receptor autoantibodies, occur in individuals with PPNAH as a manifestation of Carney syndrome and in first-degree relatives [Young et al., 1989]. It is thought that these immunogloblins may be responsible for the nodular growth and hormonal hypersecretion of the adrenal glands. The method used to measure ASI in this report was in actuality a growth assay. An increase in the percentage of cells (obtained from guinea pig adrenal slices) in the S phase, after exposure to immunoglobulin extracted from patient serum, was used as a measure of responsiveness. It is possible that the positive responses observed in cells incubated with serum from subjects with Carney syndrome were actually due to a growth-stimulating immunoglobulin not specific to the adrenal gland. These growth-stimulating immunoglobulins could be capable of stimulating growth in other organs involved in this disorder. Such specific immunoglobulins have not been described for other organ systems involved in Carney syndrome.

Growth-hormone–producing adenomas are the most frequently described pituitary tumors associated with Carney syndrome, affecting approximately 10% of all patients. About half present with gigantism and half with acromegaly [Carney et al., 1985; Kennedy et al., 1991]. A single case of a prolactinoma has been described [Handley et al., 1992]. Our patient had elevated levels of SM-C, no growth hormone suppression with glucose, no evidence of a pituitary tumor on MRI, and no clinical evidence of acromegaly. These findings are consistent with mild GH overproduction possibly secondary to somatotroph hyperplasia. Because of the aggressiveness of our patient's thyroid cancer, therapy to lower her GH and SM-C levels was considered. However, because normal GH responsiveness to oral L-DOPA was observed, therapy with bromocriptine was not considered further. Low-dose therapy with octreotide acetate (50 mg three times daily) resulted in a slight decrease in SM-C concentrations but had to be discontinued because of side effects.

Pituitary overactivity with overproduction of GH and other growth factors such as SM-C is one potential unifying explanation for neoplasia of multiple organs in

Carney syndrome [Wilsher et al., 1986]. Elevated SM-C levels were documented in a woman with Carney syndrome who declined further testing [Wilsher et al., 1986]. However, her mother and sister, who also had Carney syndrome, had normal SM-C levels. Testicular tumors, specifically Sertoli cell tumors (as in IV-9, a 9-year-old boy), and Leydig cell tumors occur in 56% of males with Carney syndrome. These tumors occur at a mean age of 16.7 years (5–33 years) [Carney et al., 1985].

Thyroid neoplasms have been reported in only 3 of 43 individuals with Carney syndrome (2 benign follicular adenomas and 1 well-encapsulated follicular carcinoma) [Carney et al., 1985]. A thyroid neoplasm composed of mixed papillary and follicular hyperplasia was reported in a 13-year-old girl with LAMB syndrome. However, this neoplasm was attributed to ionizing radiation she had received during a cardiac catheterization for cardiac myxomas [Rhodes et al., 1984]. In retrospect, this thyroid neoplasm was probably a manifestation of Carney syndrome. Because aggressive follicular carcinoma of the thyroid can be lethal [Schlumberger et al., 1986; Ruegemer et al., 1988[, open biopsy with a lobectomy and possibly a total thyroidectomy should be considered in any patient with Carney syndrome with nodular thyroid disease. To date, follicular carcinoma represents the most aggressive manifestation of Carney syndrome in our patient. It is possible that her hirsutism is of multi-factorial origin and only peripherally related to Carney syndrome. However, it is significant that she has several other relatives with hirsutism. The patient's elevated GH level and autonomous adrenal function may be contributing to the abnormality, although the adrenal androgens were actually below the normal range. Her daughter had a similar pattern of hirsutism with elevated plasma testosterone and unusually brisk response of adrenal androgens to stimulation with ACTH, suggesting different etiologies for the hirsutism.

A myxoid uterine leiomyoma, benign ovarian cystic teratomas, and ovarian cysts—but not cervical or ovarian cancer—have been described [Carney et al., 1985]. Our patient's large unusual mesenchymal cervical neoplasm may be a manifestation of Carney syndrome, but despite consultations with many pathologists, this tumor awaits further histopathological characterization and reports in other patients.

Two premalignant conditions, colonic polyps and Barrett metaplasia, that have not previously been reported in patients with this syndrome were present in our patient at an unusually young age. A review of Barrett metaplasia literature found a median age at diagnosis of 71 years, and only 2 patients were younger than 40 years of age [Khoury and Bolton, 1989]. Other series show a bimodal age distribution of Barrett esophagus with peaks at 0–15 years and again between 40 and 80 years [Spechler and Goyal, 1986]. Barrett esophagus is up to 4 times more common in men than women. Although 10–20% of all patients who have endoscopic evaluation for gastroesophageal reflux disease have Barrett metaplasia [Spechler, 1989], the rate in the fourth decade of life is only 0.3% [Cameron and Lomboy, 1992]. However, autopsy data indicate that Barrett metaplasia may be 20 times more common than estimated from clinical studies [Cameron et al., 1990].

The normal frequency of premalignant neoplastic colonic polyps in this patient's age range is unknown. Our patient's moderately sized polyp was probably present for years and must be considered an unusual finding for a woman of her age. An association of colonic polyps with Barrett metaplasia has been suggested [Sontag et al., 1985; Post et al., 1993] but may be related to genetic factors that give rise to an abnormal mucosal response to chronic injury in the gastrointestinal tract [Sontag et al., 1985].

Thus, Carney syndrome is much more than a cardiocutaneous disorder. Adding our experience from this family to that in the literature, we make the following recommendations for the management of an affected patient (beyond those stated elsewhere): periodic palpation of the thyroid gland; screening for Cushing syndrome with an overnight DST or 24-hour UFC; measurement of plasma GH, SM-C, and prolactin; a high index of suspicion for a testicular tumor in males and ovarian, uterine, and cervical lesions in females; and surveillance endoscopic procedures looking for gastrointestinal premalignant conditions. Medical evaluation of first-degree relatives is needed whenever a patient is recognized to have this autosomal dominant disorder. Further case series are needed to determine if major psychiatric disorders and congenital heart disease, as seen in this family, are part of Carney syndrome.

REFERENCES

Atherton DJ, Pitcher DW, Wells RS, MacDonald DM (1980): A syndrome of various cutaneous pigmented lesions myxoid neurofibromata and atrial myxoma: The NAME syndrome. Br J Dermatol 103:421–429.

Braithwaite SS, Collins S, Prinz RA, Walloch JL, Winters GL (1989): Decreased dehydroepiandrosterone sulfate in pigmented nodular adrenal dysplasia. Clin Chem 35:2216–2219.

Cameron AJ, Lomboy CT (1992): Barrett's esophagus: Age, prevalence and extent of columnar epithelium. Gastroenterology 103:1241–1245.

Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA (1990): Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. Gastroenterology 99:918–922.

Carney JA (1990): Psammomatous melanotic schwannoma: A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. Am J Surg Pathol 14:206–222.

Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VLW (1985): The complex of myxomas, spotty pigmentation, and endocrine overactivity. Medicine (Baltimore) 64:270–283.

Carney JA, Headington JT, Su DWP (1986a): Cutaneous myxomas. A major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. Arch Dermatol 122:790–798.

Carney JA, Hruska LS, Beauchamp GD, Gordon H (1986b): Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity. Mayo Clin Proc 61:165–172.

Carney JA, Young WF (1992): Primary pigmented nodular adrenocortical disease and its associated conditions. Endocrinologist 2:6–21.

Cheung PS, Thompson NW (1988): Carney's complex of primary pigmented nodular adrenocortical disease and pigmentous and myxomatous lesions. Surg Gynecol Obstet 168:413–416.

Cook CA, Lund BA, Carney JA (1987): Mucocutaneous pigmented spots and oral myxomas: The oral manifestations of the complex of myxomas, spotty pigmentation, and endocrine overactivity. Oral Surg Oral Med Oral Pathol 63:175–183.

Ferriman D, Gallway JD (1961): Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 21:1440–1444.

Gaillard F, Bouc M, De Lajartre AY, Audouin AF, Nomballais MF, Mussini-Montpellier J (1988): Le complexe de Carney (myxomes,

taches pigmentaires et hyperactivite endocrinienne): A propos d'une forme partielle chez des jummeaux monozygotes. Ann Pathol 8:239–243.

Handley J, Carson D, Slona J, Walsh M, Thornton C, Hadden D, Bingham EA (1992): Multiple lentigines, myxoid tumours and endocrine overactivity: Four cases of Carney's complex. Br J Dermatol 126:367–371.

Kennedy RH, Flanagan JC, Eagle RC, Carney JA (1991): The Carney complex with ocular signs suggestive of cardiac myxoma. Am J Ophthalmol 111:699–702.

Kennedy RH, Waller RR, Carney JA (1987): Ocular pigmented spots and eyelid myxomas. Am J Ophthalmol 104:533–538.

Khoury GA, Bolton J (1989): Age: An important factor in Barrett's oesophagus. Ann R Coll Surg Engl 71:50–53.

Koopman RJJ, Happle R (1991): Autosomal dominant transmission of the NAME syndrome (nevi, atrial myxoma, mucinosis of the skin and endocrine overactivity). Hum Genet 86:300–304.

Mansell PI, Higg E, Reckless JPD (1991): A young woman with spotty pigmentation, acromegaly, acoustic neuroma and cardiac myxoma: Carney's complex. J R Soc Med 84:496–497.

Post AB, Achkar E, Carey WD (1993): Prevalence of colonic neoplasia in patients with Barrett's esophagus. Am J Gastroenterol 88:877–880.

Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR (1984): Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: The "LAMB" syndrome. J Am Acad Dermatol 10:72–82.

Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JL, Offord KP, Gorman CA (1988): Distant metastases in differentiated thyroid carcinoma: A multivariate analysis of prognostic variables. J Clin Endocrin Metab 67: 501–508.

Schlumberger M, Tubiana M, Vathaire FD, Hill C, Gardet P, Travagli JP, Fragu P, Lumbroso J, Caillou B, Parmentier C (1986): Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J Clin Endocrinol Metab 63:960–967.

Siegel SF, Finegold DN, Lanes R, Lee PA (1990): ACTH stimulation tests and dehydroepiandrosterone sulfate levels in hirsute women. N Engl J Med 323:849–854.

Sontag SJ, Schnell TG, Chejfec G, O'Connell S, Stanley MM, Best W, Chintam R, Nemchausky B, Wanner J, Moroni B (1985): Barrett's oesophagus and colonic tumours. Lancet 1:946–949.

Spechler SJ (1989): Barrett's esophagus: What's new and what to do. Am J Gastroenterol 84:220–223.

Spechler SJ, Goyal RK (1986): Barrett's esophagus. N Engl J Med 315: 362–371.

Vidaillet HJ Jr, Seward JB, Fyke FE, Su WPD, Jajik AJ (1987): "Syndrome myxoma": A subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms. Br Heart J 57:247–255.

Wilsher ML, Roche AHG, Neutze JM, Synek BJ, Holdaway IM, Nicholson GI (1986): A familial syndrome of cardiac myxomas, myxoid neurofibromata, cutaneous pigmented lesions, and endocrine abnormalities. Aust NZ J Med 16:393–396.

Young WF, Carney JA, Musa BU, Wulffraat NM, Lens JW, Drexhage HA (1989): Familial Cushing's syndrome due to primary pigmented nodular adrenocortical disease: Reinvestigation 50 years later. N Engl J Med 321:1659–1664.