

Carney Triad: A Syndrome Featuring Paraganglionic, Adrenocortical, and Possibly Other Endocrine Tumors

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Background: Two young women, each with paraganglioma and gastric stromal tumor, were encountered in the middle 1970s. One also had an adrenal cortical adenoma and the other pulmonary chondroma.

Objective: To test the hypothesis that the combination of tumors might represent a rare syndrome, similar cases were searched for. Five additional patients with gastric stromal tumor, paraganglioma, and pulmonary chondroma were found, and all were young women. None had a family history of the tumors. The combination of the three tumors was later referred to as the Carney triad.

Features of the Syndrome: Among 77 patients with the syndrome, 85% were women and 15% were men. Onset ranged from 7 to 48 yr (mean, 20 yr). The gastric lesion was usually the presenting tumor (75%), followed by the lung lesion (15%) and the paraganglionic tumor (10%). Twenty percent of the patients had adrenocortical adenoma(s), and 10% had esophageal leiomyoma(s). All the tumors were multifocal. The gastric and paraganglionic tumors metastasized in one third and one tenth of the patients, respectively. The pulmonary tumors were asymptomatic and benign.

Follow-up: At follow-up, 80% of the patients were alive, two thirds with pulmonary chondroma, 25% with metastatic or residual gastric stromal tumor, and 5% with primary or metastatic paraganglioma. Twenty percent of the patients were dead, usually from metastatic gastric stromal tumor, less frequently from metastatic paraganglioma.

Conclusion: The Carney triad is a chronic, persistent, indolent but sometimes fatal disorder of unknown etiology. (*J Clin Endocrinol Metab* 94: 3656–3662, 2009)

Carney triad (hereinafter referred to as “the triad”) is a syndrome of tumors affecting at least five organs, the stomach, the lung, the paraganglionic system, the adrenal (cortex and medulla), and the esophagus. The stomach features gastrointestinal stromal tumor (GIST), the lung chondroma, the paraganglionic system paraganglioma, the adrenal adenoma and pheochromocytoma, and the esophagus leiomyoma. The tumors are multiple in each of the organs. The disorder mainly affects young women. It is a chronic, persistent, and generally indolent condition with a long natural history. The etiology of the syndrome is unknown, but its cause is likely genetic.

Background

Patients with two or more different neoplasms are not uncommon; the concurrence of the lesions is likely fortuitous in most cases; finding a connection between the tumors, if one existed, could be difficult or impossible. But if 1) the concurrence of the tumors was statistically unlikely even in one patient because of their rarity; 2) the neoplasms were multiple in the affected organs; 3) the lesions appeared at an age when tumors were not expected; and 4) the association had a pronounced sex predilection, then a case could be made for concluding that the concurrence of the tumors was likely not coincidental. On the basis of evidence of this type, it was concluded in 1977 that

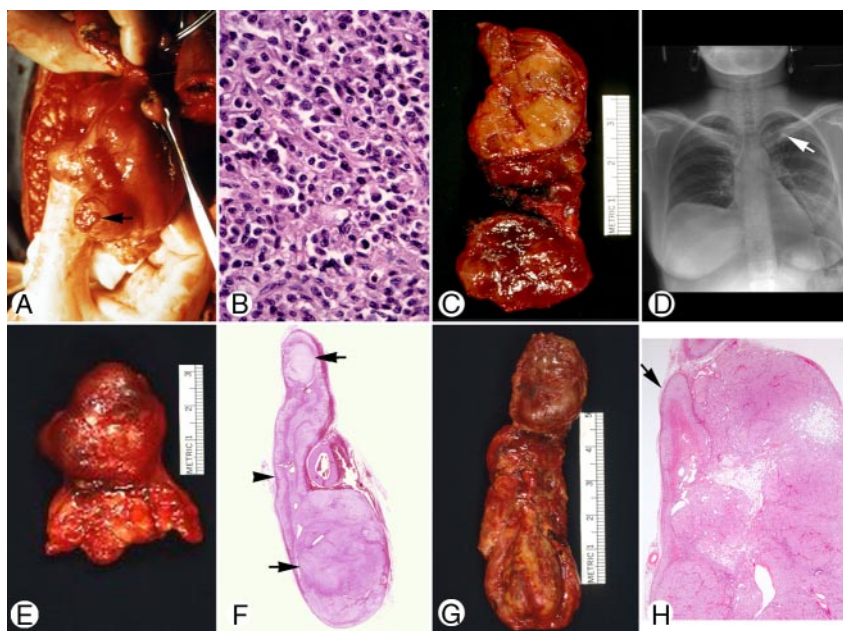


FIG. 1. Case 1. A, Multiple tumors with secondary excrescences protruded from the gastric serosal surface. B, GIST featured a sheet of round and polygonal epithelial-like cells with granular eosinophilic cytoplasm and nuclei with mild irregularity. C, Dumbbell-shaped aortopulmonary paraganglioma had an intrapericardial component. D, Calcified nodule consistent with pulmonary chondroma in the left upper lobe (arrow). There was elevation of the right diaphragm. E, Extraadrenal paraganglioma intimately associated with the right adrenal gland. F, Two cortical adenomas in the right adrenal gland (arrows). The extratumoral cortex (arrowhead) showed normal zonation and was 0.9 mm thick (normal thickness, ~1 mm). G, Extraadrenal paraganglioma (upper mass) attached to an enlarged left adrenal gland that contained a pheochromocytoma. H, Lobulated pheochromocytoma in the left adrenal gland. The cortex (arrow) showed normal zonation.

association of gastric GIST, paraganglioma, and pulmonary chondroma constituted a rare syndrome.

Interest in the entity was initially sparked by a perceived similarity of the initial two cases to the classical multiple endocrine neoplasia (MEN) syndromes (1–3), disorders that featured multiple endocrine neoplasms, including pituitary adenoma, parathyroid adenoma, islet cell adenoma, adrenal cortical adenoma, carcinoid tumor, medullary thyroid carcinoma, and pheochromocytoma (adrenal paraganglioma). MEN2B (4), one of the syndromes, also included nonendocrine tumors, mucosal neuromas, and congenital anomalies, including marfanoid habitus and other connective tissue abnormalities. The MEN neoplasms were multicentric and multifocal; the disorders were familial, transmitted as autosomal dominant traits; the sexes were generally equally affected; and the disorders were frequently evident at a young age.

Two Unusual Cases

In 1975, histological slides from an unusual case were sent to Mayo Clinic for a second opinion. The patient, a 15-year-old girl (case 1) (Fig. 1), was found to be hypertensive

(150/110 mm Hg) and anemic (hemoglobin, 560 mmol/liter) at a school physical examination. Laboratory investigations and imaging studies led to diagnoses of pheochromocytoma and gastric tumors. At laparotomy, two different endocrine tumors, paraaortic paraganglioma (three lesions) and adrenal cortical adenoma, and a nonendocrine neoplasm, multifocal gastric GIST, were found. Later, at age 26, the patient had an aortopulmonary paraganglioma resected. At age 27, four nodular filling defects were found in the esophagus. At age 29, she underwent bilateral adrenalectomy for juxtaadrenal paragangliomas, unilateral pheochromocytoma, and a cortical adenoma. At age 46, two calcified lung lesions were found.

The following year, 1976, a patient with similar findings attended Mayo Clinic. The 25-yr-old woman (case 2) (Fig. 2) had multiple paragangliomas, the first at age 11, two types of nonendocrine tumor, gastric GIST and pulmonary chondroma, both multifocal, and congenital deformity of the external and middle ears. At age 49, she had

a cortisol-secreting adrenal adenoma that caused subclinical Cushing syndrome.

At initial presentation, both of these patients manifested multifocal paraganglioma and multifocal gastric GIST, one had an adrenal cortical adenoma, and the other had multifocal pulmonary chondroma and a bilateral congenital abnormality, and both were young. The concurrence of endocrine and nonendocrine tumors in the two young patients, one having with a congenital abnormality, was vaguely reminiscent of MEN2B in which endocrine and nonendocrine tumors and congenital anomalies occur. Enquiry, stimulated by the findings in the second case, revealed no relative of either patient with any of the tumors mentioned or congenital abnormalities. The notion of a familial MEN2B-type disorder was apparently incorrect. But the unusual findings in the two patients could not be dismissed without further investigation.

More Cases Found

Search of the Mayo files and the world literature in 1976 revealed five other individuals with combinations of paraganglioma, gastric GIST, and pulmonary chondroma, two

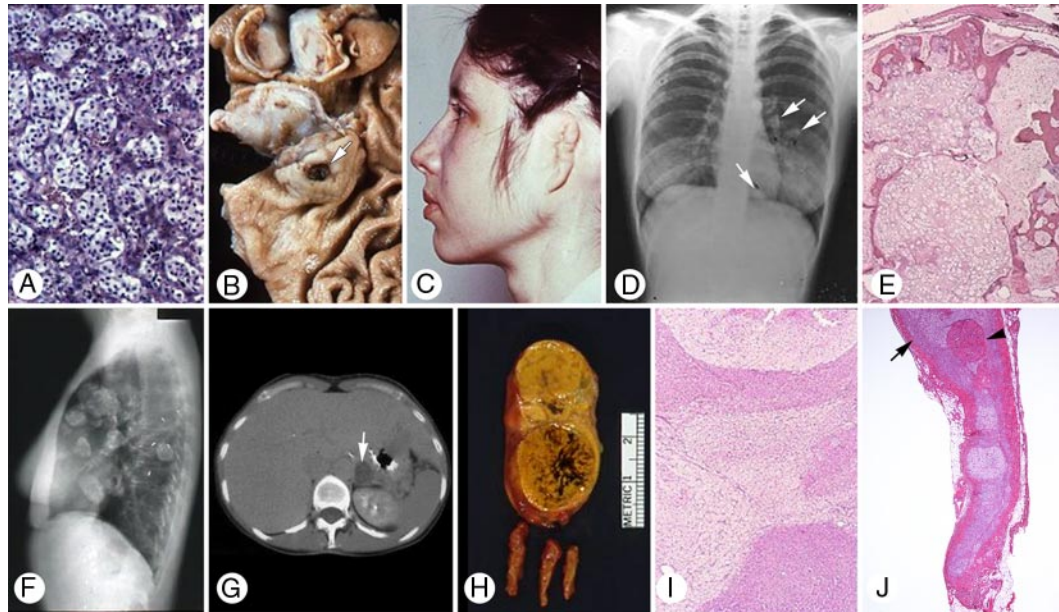


FIG. 2. Case 2. A, Carotid body tumor featured cells with clear cytoplasm arranged in clusters (*zellballen*) supported by vascular stroma. B, Stomach with two submucosal sectioned GISTs, one with ulceration (*arrow*). C, Congenital deformity of the left auricle. The scar from carotid body surgery was barely visible. D, Chest x-ray showed multiple calcified lesions in the left lung (*arrows*). E, Pulmonary chondroma was composed of well-differentiated cartilage and bone and limited by a thin pseudocapsule. F, Chest x-ray showed multiple calcified pulmonary lesions. G, Computed tomography showed enlargement of the left adrenal gland (*arrow*). H, Left adrenal gland showed two juxtaposed neoplasms, the upper one yellow, the lower one dull yellow with brown and black zones. Slices of the extratumoral cortex showed a very thin yellow cortical rim around the medulla. There was no zona reticularis visible. I, The lower tumor in panel H had two populations of cells, one with clear cytoplasm, the second with granular eosinophilic (*pink*) cytoplasm. J, The extratumoral cortex (*arrow*) seen in panel H measured 0.2 mm in thickness (normal, ~1 mm) and was composed of small cells with eosinophilic cytoplasm. There was no zona reticularis. Two cortical clear-cell nodules were present. The pink mass (*arrowhead*) was hypertrophied smooth muscle of tributary of central vein.

in the Mayo files and three in the literature (5). The patients were all young women; none had a similarly affected relative. The findings in the seven patients were persuasive that the three tumors constituted an entity, a conclusion that was reported in 1977 under the rubric “The triad of gastric leiomyosarcoma, functioning extraadrenal paraganglioma, and pulmonary chondroma.” Gastric epithelioid leiomyosarcoma was the term in use at the time for what today is referred to as gastric GIST. Previously, the tumor had been referred to as bizarre leiomyoma and leiomyoblastoma.

The combination of the three tumors was clearly not a MEN syndrome in the classical sense—endocrine tumors were not the dominant tumors in most cases and the disorder was not familial—but neoplasms had occurred multifocally in at least two endocrine organs in young patients and, in this, the triad resembled an MEN syndrome. In 1982, the eponymic title “Carney’s triad” (6) was used for the tumor combination.

The Triad Is Usually Only Partially Expressed

By 1999, 72 new patients with the triad had been recognized (7). At presentation, one patient had all three tu-

mors, one third had two of the three, and the remainder had one of the tumors. The gastric tumor was the commonest presenting lesion (75%), followed by the lung (15%), and paraganglionic tumors (10%). The mean interval between detection of the first and second tumor was about 8 yr; the five longest intervals were 21, 21, 24, 24, and 25 yr. Most of the patients manifested only two of the three tumors, indicating that the syndrome was usually incompletely expressed; it is possible that some of these will eventually develop the third neoplasm. It also seems likely that there are patients with only one component who will never exhibit any of the others. Patients with any of the three tumors multifocally should be considered at risk for the others, particularly if young and female.

Of the 79 patients (the original seven and the newly identified 72), 85% were women and 15% were men. The age of onset (designated as the date of histological diagnosis of the first component) ranged from 7 to 48 yr (mean, 20 yr). Onset was before age 30 yr in 80% of patients and after 40 yr in 5%. In 25% of the patients, clinical or radiological evidence of one of the tumors antedated the onset by 1 to 26 yr (mean, 7 yr).

One fourth of the patients had the three tumors; one half had the gastric and pulmonary tumors; the remaining one fourth had paraganglionic and the gastric tumors.

One patient had an unaffected identical twin. Another had a brother with a major congenital defect of an upper limb who died at age 40 of pancreatic adenocarcinoma. And a third patient had a child with congenital adrenal hyperplasia, a second with congenital cataracts, and a third with maldevelopment of the motor cortex.

Significance of Concurrence of Paranglioma and Gastric GIST

Nineteen patients had the paraganglioma and gastric GIST combination; 17 of them had no family member with either tumor. But two did—each had a sibling with paraganglioma, raising the possibility that the triad might possibly be familial after all. If it was, the pattern of inheritance was not apparent because none of the 355 primary relatives of the remaining 77 patients had any of the triad components.

After 1999, several new patients with findings related to or suggestive of the triad came to attention. One was a young man with multiple paragangliomas and multiple gastric GISTs whose sister had bilateral carotid body paragangliomas. Another was a woman with bilateral carotid body tumors and gastric GISTs, who had a sister with carotid body tumors and a functioning pheochromocytoma. The third was a young man with gastric GISTs whose paternal uncle and aunt had paraganglioma. Observations in these five kindreds (the two mentioned in the previous paragraph and the three just described) led to recognition of a new autosomal dominant syndrome of paraganglioma and gastric GIST with variable penetrance (8) that was distinct from the triad, and later shown to be caused by a germline mutation of the genes encoding succinate dehydrogenase subunits, *SDHB*, *SDHC*, and *SDHD* (9, 10). A clue to the familial paraganglioma-gastric GIST syndrome is that paraganglioma is the presenting tumor, unlike the triad in which the gastric tumor is usually the lesion initially recognized. Thus, when paraganglioma and gastric GIST are found in a patient or in members of a family, there are at least two possible explanations for the concurrence. The other two combinations of the triad tumors, gastric GIST and pulmonary chondroma, and pulmonary chondroma and paraganglioma, still warranted a diagnosis of incomplete expression of the triad.

None of the 17 other patients with paraganglioma and GIST mentioned earlier have been tested for the *SDH* gene mutations. But because each presented with the gastric tumor and had no similarly affected family member, the likelihood is that they have the triad.

Additional Endocrine and Nonendocrine Components

Findings in the 70 new patients and follow-up in the original seven revealed additional components of the triad, adrenal cortical adenoma and esophageal leiomyoma. Two other endocrine tumors were found in the group, parathyroid adenoma (two patients, one had two-gland disease) that caused primary hyperparathyroidism, and esophageal carcinoid tumor. Primary hyperparathyroidism is a common condition; its occurrence in the two patients may have been coincidental. But esophageal carcinoid is a very rare tumor, and its appearance in an 18-yr-old patient with the triad cannot be dismissed as being coincidental at this point. Thus, the condition initially reported as a triad of tumors is at least a pentad. The presence of any two of the five tumors multifocally in a young patient warrants a presumptive diagnosis of incomplete expression of the triad.

Features of the Five Tumors

GIST

GIST occurs as a sporadic tumor and as a component of several familial syndromes. The sporadic gastric neoplasm is a single tumor with a benign course usually found in an older patient (median age, 65 yr) (11). It is caused by mutation of the *KIT* gene, uncommonly by a *PDGFRA* gene mutation (12, 13). The syndromic tumor is transmitted as an autosomal dominant trait (14–17). The triad is an exception to this. Although the triad GIST is similar microscopically to the sporadic lesion, it has so many pathological, behavioral, and molecular genetic differences from the sporadic lesion that it is misleading to label it as GIST. Gastric stromal sarcoma (GSS) is a more accurate title and will be used for it henceforth in this article.

In the triad, most of the GSSs came to attention because of mucosal ulceration caused by the tumors. The ulceration resulted in bleeding with consequent anemia, melena, hematemesis, and combinations of these. Occasionally, an asymptomatic upper abdominal mass was palpated, and a few GSSs were found during investigation for other conditions. The youngest and oldest patients at detection of the neoplasm were 7 and 48 yr old, respectively (mean age, 20 yr). Imaging studies showed one or more gastric filling defects, sometimes with evidence of ulceration. Gastroscopy commonly revealed antral submucosal masses along the lesser curvature where interstitial cells of Cajal (ICCs) (see next paragraph) are maximally concentrated (18).

The GSSs were treated by segmental resection(s), partial gastrectomy, and total gastrectomy. Adjuvant ther-

apy, including radiation, chemotherapy, and hyperthermia, was ineffective for the primary tumor and its metastases. Imatinib mesylate, a successful therapy for sporadic GIST and its metastases (19), was also ineffective or produced borderline decrease in tumor size.

Pathologically, the stomach showed multiple, large, circumscribed, intramural tumors that caused polypoid intraluminal and serosal protrusions (Figs. 1A and 2B). The polygonal tumor cells (Fig. 1B) shared morphological and immunohistochemical features (CD117 and CD34 immunopositivity) with the ICCs. Because of this, the gastric tumors are believed to arise from ICCs or related cells. ICCs are associated with the myenteric plexus and believed to be the pacemaker cells of the gut. The GSSs did not exhibit the *KIT* or the *PDGFRA* gene mutations found in sporadic GIST (11). Metastasis occurred in one third of the patients to the liver, gastric lymph nodes, and peritoneum. Extraabdominal metastasis to lung, brain, and bone was rare and was fatal.

New GSSs developed in the gastric remnant in half of the patients who had less than total gastrectomy, requiring one or more additional gastric operations. The interval between primary surgery and recurrence ranged from 1 to 36 yr (mean, 12 yr). The five longest intervals were 23, 27, 28, 34, and 36 yr.

Pulmonary chondroma

Because of its great rarity, pulmonary chondroma was a scarcely known tumor until it was found to be a component of the triad (5, 7, 20). This rarity contributed to common misinterpretation of the neoplasm as pulmonary hamartoma by radiologist and pathologist. Pulmonary hamartoma is almost always a solitary tumor in older patients, usually men (21). It contains bronchial epithelium which pulmonary chondroma does not, the important distinguishing feature between the two tumors. The histogenesis of the chondroma is unknown. Some of the tumors contain foci of well-differentiated mesodermal spindle cells resembling fibroblasts that seem to differentiate into the polygonal matrix-producing cells and may be the precursor cells of the neoplasm.

Three fourths of patients had pulmonary chondroma(s) (Fig. 2E). The earliest and latest ages at detection of the neoplasm were 12 and 49 yr (mean, 24 yr), respectively. A single tumor, multiple unilateral tumors, and bilateral tumors were present in 40, 25, and 15% of the patients, respectively, without predilection for lung or lobe. The neoplasms caused no symptoms and were usually found during the search for metastases after discovery of the gastric tumor. In the past, some of the neoplasms that were not biopsied were mistakenly treated as GSS metastases

with chemotherapy. When the lesions failed to respond, excision or biopsy of the lesions revealed their true nature.

Chest radiographs showed multiple circumscribed tumors, often with popcorn-type calcification, scattered in the lungs (Fig. 2, D and F). When calcified, the appearance of individual tumors was indistinguishable from that of pulmonary hamartoma. The tumors usually measured several centimeters in diameter and ranged up to 9 cm. When they were the presenting lesion in the triad and had not become calcified, and biopsy revealed their cartilaginous nature, they were sometimes misinterpreted as metastatic chondrosarcoma, and bone scans were performed in search of a bone primary.

The chondromas were well-circumscribed, bluish, lobulated lesions that were easily enucleated from the pulmonary parenchyma when superficially located in the lung. Microscopically, they were composed of mature cartilage with varying amounts of bone and sometimes a minor component of spindle cells.

Because they did not cause symptoms or impair lung function and grew very slowly, treatment was not deemed necessary, once their nature and significance was known. In 1976, a patient (case 2) had five lung lesions excised; clinically, they had been thought to be metastatic GSS; they were in fact chondromas. Presently, she has at least 20 asymptomatic bilateral calcified lung tumors (Fig. 2F). The natural history of the chondromas remains to be fully determined. It is likely that some of them will continue to enlarge slowly. Others may ossify and cease to grow.

Paraganglioma

Paraganglioma is a rare tumor. It arises in minute bodies, the paraganglia, that form a dispersed neuroectodermal organ system extending from the base of the skull to the sacrum, associated with the sympathetic and parasympathetic nervous system. The adrenal medulla is the largest paraganglion in the body. The tumors are very vascular lesions composed of chromogranin-positive cells arranged in clusters (Fig. 2A) surrounded by S100-positive sustentacular cells.

About half of the patients had one or more extraadrenal paragangliomas at ages ranging from 12 to 61 yr (mean, 27 yr). Six had pheochromocytoma, bilateral in one. Two thirds of the paragangliomas were symptomatic. Manifestations (in order of frequency) were: 1) symptoms and signs of catecholamine excess; 2) pressure symptoms (dyspnea, nerve paralysis, tinnitus); and 3) an asymptomatic imaged or palpable tumor. The tumors were about equally distributed in the head and neck, thorax, and abdomen. The aortopulmonary body was a common site of the tumor (Fig. 1C), and several were located in the heart. Metastasis occurred in 10% of the patients.

Measurement of plasma and/or 24-h urinary fractionated metanephrines or catecholamines detected functioning tumors. Lesions amenable to excision, including carotid body and retroperitoneal tumors, were cured. The retroperitoneal tumors were occasionally so intimately associated with the adrenal gland that adrenalectomy was unavoidable for their removal. Some mediastinal and base of skull lesions were unresectable and were treated with radiation or polyvinyl alcohol particle embolization.

Three patients died from paraganglioma, two from unresectable tumor (aortopulmonary and vagal body lesions), and one from metastasis. Ten percent of the patients were alive with unoperated, inoperable, or metastatic paraganglioma.

Adrenocortical adenoma

One fifth of the patients had a clinically nonfunctioning adrenal tumor that was usually interpreted as an incidentaloma, less frequently as a nonfunctioning pheochromocytoma. The tumor was commonest in the third and fourth decades and was found during gastric imaging studies or at surgery for GSS. Computed tomography imaging usually revealed a homogeneous mass with a smooth border and a low attenuation value. The neoplasms were unilateral and single or multiple, or bilateral, and ranged in size from 0.4 to 4 cm. When adrenocortical function was tested, the results were normal. One half of the lesions were excised. Pathologically, the tumors were yellow, circumscribed, and composed of large, clear lipid-rich vacuolated cells; the extratumoral cortex was normal. The neoplasms were indistinguishable from sporadic nonfunctioning cortical adenomas.

One of the adenomas, however, caused subclinical Cushing syndrome. The patient (case 2) who had no clinical evidence of Cushing syndrome was reoperated at age 48 yr for GSSs in the stomach remnant and removal of a 4-cm left adrenal tumor that had been interpreted as an incidentaloma. Urinary free cortisol levels were normal 15 months preoperatively. The resected adrenal gland showed the following: 1) a 1.7-cm yellow tumor, consistent with a nonfunctioning adenoma; 2) a 2-cm tumor with a variegated appearance, dark yellow with brown and black zones and streaking; and 3) a very thin extratumoral cortex with no zona reticularis visible (Fig. 2, H–J). The latter two findings were typical of a cortisol-producing neoplasm. Because of them, intraoperative steroid support was administered. Postoperatively, subclinical Cushing syndrome was confirmed biochemically. The findings in this patient emphasize the importance of evaluating cortical functional activity of incidentalomas in the triad (22). The fate of the unresected incidentalomas remains to be learned; with continued growth, some may

become functional. Certain of the patients with unilateral lesions likely will develop contralateral adrenal cortical tumor(s).

Esophageal leiomyoma

The leiomyomas were small asymptomatic sessile or pedunculated polypoid lesions that were usually found during upper endoscopy for the GSSs. Presumably, the lesions arose from smooth muscle cells of the muscularis propria or muscularis mucosae. Microscopically, they were circumscribed lesions composed of well-differentiated spindle cells arranged in interlacing fascicles and bundles. The cells exhibited immunopositivity for actin and desmin and markers of normal smooth muscle cells, and they were negative for CD117 and CD34, markers of ICCs and GSS.

The natural history of the lesion is unknown. In one patient (case 1), esophageal lesions found when the patient was 26 remained asymptomatic until death of the patient (from GSS) 19 yr later. Another patient, a 16-yr-old girl, had a single episode of vomiting. Investigation revealed dilatation of the proximal two thirds of the esophagus and multiple filling defects, interpreted as leiomyomas. The patient refused surgical intervention and had no further symptoms. She died at age 53 of lung carcinoma. Thus, the esophageal tumor may have a limited potential for growth.

Other Conditions in the Patients

Other conditions in the patients included mammary adenocarcinoma (four patients), renal cell carcinoma (two patients, aged 26 and 37 yr, respectively), renal angiomyolipoma (one patient), bony exostoses (two patients), thyroid adenomas (two patients), branchial cleft cysts (three patients), arthritis (four patients), and colonic adenocarcinoma (one patient).

Follow-Up

Follow-up of the cases ranged from 5 to 60 yr (mean, 22 yr). About 80% of the patients were alive, two thirds with pulmonary chondroma(s), one fourth with metastatic or residual primary GSS, and 5% with primary or metastatic paraganglioma. Some patients were well years after removal of hepatic and peritoneal GSS metastases. Others with considerable intraabdominal metastatic GSS were asymptomatic. About 20% of the patients were dead, one half due the triad, usually from hepatic, peritoneal, and extraabdominal metastatic GSS, less frequently from met-

astatic paraganglioma; the remainder succumbed to non-triad causes but with elements of the triad.

Etiology

The triad is generally accepted to be a genetic disorder. One patient, it will be recalled, had an unaffected identical twin suggesting that the syndrome may be caused by a postzygotic mutation. Positional cloning of the responsible gene(s) is not possible because families are not affected. To date, no coding sequence mutations of the *KIT* and *PDGFRA* genes or the *SDHB*, *SDHC*, and *SDHD* genes that are responsible for sporadic GIST and familial paraganglioma, respectively, have been found (23). The most frequent and greatest contiguous change detected by comparative genomic hybridization was deletion of the 1cen-q21 (23). Thus, initial attempts to identify the cause of the triad have ruled out certain molecular genetic possibilities but the responsible gene(s) remains unknown.

Acknowledgments

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Disclosure Summary: The author has no conflict to declare.

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