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Gastric Stromal Sarcoma, Pulmonary Chondroma, and Extra-adrenal Paraganglioma (Carney Triad): Natural History, Adrenocortical Component, and Possible Familial Occurrence

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• ***Objective*: To investigate the natural history of the triad of gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma, a rare syndrome of unknown cause primarily affecting young women.**

• ***Methods*: Mayo Clinic records, the world literature, and the author's files were searched for patients with all or 2 of the 3 tumors.**

• ***Results*: Seventy-nine patients, 67 women and 12 men, were identified, 17 (22%) with the 3 tumors and 62 (78%) with 2 tumors. Forty-two (53%) had gastric and pulmonary tumors, the most common combination. The longest interval between detection of the first and second components was 26 years (mean, 8.4 years; median, 6 years). Follow-up ranged from 1 year to 49 years (mean, 20.6 years; median, 20 years). Sixty-four patients (81%) were alive, 19 (24%) apparently free of disease and 45 (57%) with residual or metastatic tumors. Thirty-two patients (41%) had had 1 or more local recurrences of the gastric sarcoma; the longest interval to first recurrence was 36 years. Twenty-one survivors (27%) had hepatic metastatic gastric sarcoma with follow-up of 1 year to 25 years (mean, 9.3 years; median, 7 years). Fifteen patients (19%) were dead, 10 (13%) of whom died of the disorder. Ten patients (13%) had nonfunctioning adrenocortical tumors. Two patients each had a sibling with 1 component of the triad.**

• ***Conclusions*: The triad is a chronic, persistent, and indolent disease. Benign adrenocortical tumors are a component of the condition. The disorder may be familial.**

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^{131}I MIBG = radioactive iodine–metaiodobenzylguanidine

In 1977, Carney et al[1] reported the association of gastric (epithelioid) leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma (herein referred to as "the triad") in 2 patients and 2 of the 3 tumors in 5 other patients, all unrelated young women. One patient[2] also had a nonfunctioning adrenocortical adenoma. The tumor pattern—multifocal lesions in multiple organs in young patients—suggested an inherited disorder, but such was not found.

In 1983, Carney[3] reviewed findings in 24 affected patients (including 2 males), 6 of whom had the 3 tumors. The gastric neoplasm had metastasized in 8 patients, demonstrating its malignant nature, but its behavior was indolent in comparison with that of the sporadic neoplasm, an aggressive tumor, once metastasis had occurred.[4] Some of the paragangliomas were nonfunctioning in the new patients, none of whom at that time had an adrenocortical tumor. There were no familial cases.

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Since 1983, 48 additional patients have been recognized. This article reports findings in the 79 patients, provides insight into the natural history of the triad, identifies adrenocortical adenoma as a component of the disorder, and raises the possibility that the syndrome may be familial.

METHODS

Records of the Mayo Clinic, Rochester, Minn, the world literature, and the author's files were searched for patients with 2 or more of the following: (1) gastric leiomyoblastoma, gastric leiomyosarcoma, gastric epithelioid leiomyosarcoma, gastric stromal tumor, gastric plexosarcoma, or gastric autonomic nerve tumor; (2) pulmonary chondroma, pulmonary hamartoma, or pulmonary osteochondroma; and (3) extra-adrenal paraganglioma or pheochromocytoma (adrenal paraganglioma). Seventy-nine cases were identified, 12 from Mayo Clinic records, 45 from the literature,[5-61] and 22 from the author's files. Clini-

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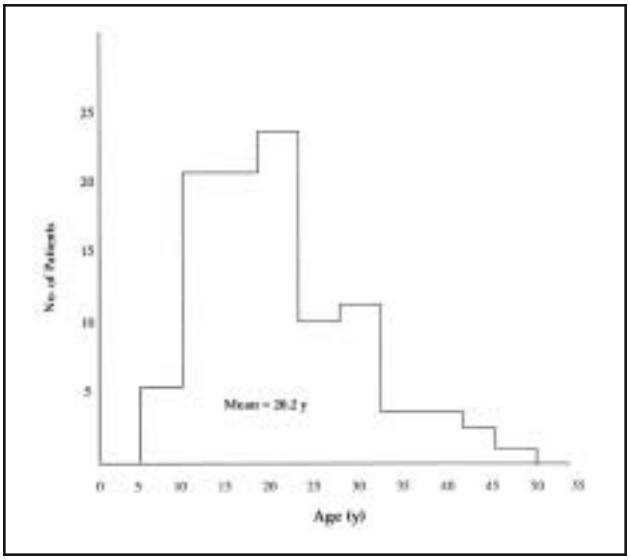

Figure 1. Age at onset of the triad in 79 patients.

cal, pathological, and follow-up data were sought in the cases. Histological slides were reviewed in 71 cases (90%).

RESULTS

Clinical Findings

Patients.—The patients were 67 women (85%) and 12 men (15%) from all continents except Africa. None was black (1 patient was erroneously reported as such[43]). None was related. Forty-one patients had 103 children (maximum, 9) after onset of the disorder.

Age.—Age at onset (designated as the date of histological diagnosis of the first component) ranged from 7 to 48 years (Figure 1). Onset was before the age of 30 years in 65 patients (82%) and after the age of 40 years in 5 (6%). Table 1 displays the presenting component and associated findings. Manifestations of the tumors antedated onset in 21 patients (27%) between 1 year and 26 years (mean, 6.7 years; median, 4 years).

Table 1. **Presenting Symptoms and Signs Among 79 Patients***

Tumors		No. (%) of patients
Gastric stromal sarcoma		58 (73)
Anemia (+ or – melena)	24	
Hematemesis (+ or – melena)	14	
Serendipitous (6) or unknown	7	
Epigastric pain, nausea, vomiting	6	
Intra-abdominal or intumoral hemorrhage	4	
Asymptomatic abdominal mass	3	
Pulmonary chondroma		12 (15)
Asymptomatic radiographically evident pulmonary mass or masses	12	
Paraganglioma		8 (10)
Symptomatic or asymptomatic masses	4	
Hypertension	4	

*One patient[14] presented with vomiting due to an esophageal tumor (not resected). + = present; – = absent.

Combinations of Tumors.—Table 2 presents the tumors in the patients. At onset of the syndrome, all 3 tumors were detected in 1 patient (1%), 2 tumors in 27 (34%), and 1 tumor in 51 patients (65%). The mean interval between detection of the first and second tumors was 8.4 years (median, 6 years); the 5 longest intervals were 21, 21, 24, 24, and 26 years. The longest interval between detection of the second and third tumors was 18 years (mean, 5.9 years; median, 7 years).

Other Findings.—Ten patients (13%) had nonfunctioning adrenocortical adenomas, bilateral in 1, unilateral and multifocal in 3 (Figure 2), and single in the rest. One patient had bilateral adrenal nodules that measured 12, 6, and 4 mm in diameter. Two other patients each had an unresected adrenal tumor. Seven patients (9%) had esophageal tumors that were excised in 4 patients (leiomyoma in 3, stromal tumor in 1). One unresected tumor had been present for 37 years,[14] and another had not changed in size for more than 6 years.[37] The tumors were asymptomatic except in 1 case.[14] They were identified during endoscopic or radiographic examination for the gastric tumors. They ranged in diameter from 1 to 2 cm and occurred in the proximal, middle, and distal esophagus. Endoscopically, they were polypoid or "wormlike," submucosal, and not ulcerated. One patient had 2 tumors, and there were probably 2 in a second patient. Seven patients had proximal duodenal stromal tumors, which were multiple in 3 patients, and 1 patient had a proximal small intestinal stromal tumor and an esophageal leiomyoma.[54] Carcinoma (pulmonary, gastric [at gastroenteric anastomosis 38 years after subtotal gastrectomy], and abdominal [primary site unknown]) occurred in 3 patients. Two patients also had bony exostosis, and 1 patient each had cutaneous lipomas, bilateral ear deformity, branchial cleft cyst, renal angiomyolipoma, 2 parathyroid adenomas, gluteal myxoma and dilated cardiomyopathy, and uterine leiomyosarcoma.

Gastric Stromal Sarcoma

Symptoms and Signs.—The symptoms and signs are presented in Table 1. The lesion was found at surgery in 76 patients and at autopsy in 2.

Location and Configuration.—Gastroscopy (24 cases) revealed 1 or more sessile, polypoid, submucosal, ulcerated masses, usually in the antrum close to the lesser curvature. Radiographic examination (35 cases) showed smooth, round or oval tumors with filling defects, generally in the distal stomach (Table 3).

Primary Surgery.—Subtotal gastrectomy, segmental resection(s), and total gastrectomy were performed in 50, 14, and 12 patients, respectively. Twenty-one patients (28%) had gross metastasis to 1 or more sites: gastric lymph nodes (14 patients), peritoneum (7), and liver (5).

Pathological Findings.—Multiple, polypoid intramural, ulcerated tumor masses, ranging in size from 0.4 cm in diameter to 8.5 x 5.5 x 4.5 cm, were located mainly in the antrum and on the lesser curvature. Bosselated serosal masses with secondary and tertiary bleblike nodules were common. Microscopically, polygonal and fusiform cells were arranged in sheets, clusters, and fascicles. Micrometastases were found in gastric lymph nodes in 4 patients.

Results of Primary Surgery.—Locally recurrent tumors developed in 23 patients (46%) after subtotal gastrectomy (in this article, "recurrent" designates a newly occurring tumor, not regrowth of a previously incompletely excised one). Among 12 patients who had segmental resection, the tumor was incompletely resected in 2, requiring additional gastric resection in 1 and total gastrectomy in the other. In 9 (90%) of the remaining 10 patients, additional tumors developed. One patient who had total gastrectomy had recurrence at the esophagoenteric anastomosis.

Secondary and Tertiary Surgery.—Thirty-two patients (41%) had secondary surgery and 8 (10%) had tertiary surgery for additional gastric recurrence. The interval to recurrence ranged from 1 year to 36 years (mean, 12.4 years; median, 12 years); the longest 5 intervals were 23, 27, 28, 34, and 36 years. The interval between primary and tertiary surgery ranged from 5 to 39 years (mean, 18.8 years; median, 16.5 years). Metastasis was found in 22 patients (28%) to 1 or more intra-abdominal sites (liver, 14 patients; peritoneum, 10; gastric lymph nodes, 6), resulting in an overall rate of metastasis of 55%. Hepatic metastatic lesions were found in 1 patient 33 years after primary surgery. Two patients (3%) had extra-abdominal metastasis, to lung, bone, and skin in one and to skeletal muscle in the other; both died of the disorder.

Pulmonary Chondroma

Sixty patients (76%) had pulmonary chondromas, diagnosed histologically and radiologically in 45 and 15 patients, respectively. The earliest and latest ages at detection were 12 and 49 years, respectively (mean, 23.7 years; median, 21 years). A 48-year-old patient with a calcified lung nodule had normal radiographic findings at the age of 45 years. The neoplasms usually were detected during evaluation for the gastric neoplasm and often were misinterpreted as metastatic sarcoma and treated as such.

Symptoms, Signs, and Radiographic Findings.—The tumors were asymptomatic, with 1 exception[37]: this patient had virtual replacement of a lung by confluent calcified chondromas.

Table 2. **Tumor Combinations Among 79 Patients***

Gastric sarcoma	Pulmonary chondroma	Extra-adrenal paraganglioma	No. (%) of patients
+	+	+	17 (22)
+	+	–	42 (53)
+	–	+	19 (24)
–	+	+	1 (1)

*+ = present; – = absent.

One tumor, multiple unilateral tumors, and bilateral tumors occurred in 31 (39%), 19 (24%), and 10 (13%) patients, respectively, without predilection for lung or lobe. Lesions were calcified initially in 27 patients (45%) and became so later in 6 patients (10%). Interpretations included metastatic neoplasm, indeterminate nodule, and pulmonary chondroma or hamartoma in 15, 13, and 7 patients, respectively.

Surgery.—Forty-one patients (68%) underwent thoracotomy. The operations included tumor enucleation in 9 patients, segmental or wedge resection in 13, lobectomy in 17, and unknown procedure in 2. Eleven patients (27%) had 2 thoracotomies, and 2 (5%) had 3 for recurring chondromas.

Pathological Findings.—The lung tumors were circumscribed, had a hard to soft consistency, and measured 0.5 to 12 x 10 x 10 cm. The cut surface appeared cartilaginous, bony, or gelatinous. Microscopically, a mixture of mature cartilage, bone, and stellate mesenchymal cell set in a myxoid stroma was seen.

Results of Surgery.—Pulmonary surgery was curative in 18 patients (44%). Follow-up ranged from 1 year to 30 years (mean, 13.4 years; median, 13 years). One or more new tumors developed in 23 patients (56%).

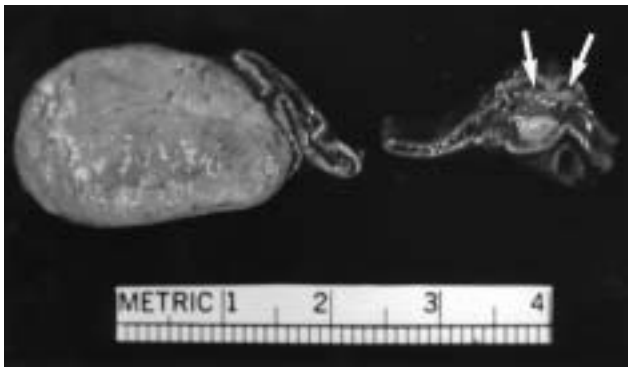

Figure 2. Cut surfaces of 2 slices of adrenal gland showing a circumscribed adenoma in one and multiple small adenomas (arrows) in the other. Additional slices revealed 3 more small adenomas. Thickness of the extratumoral cortex is normal.

Table 3. **Location of Gastric Stromal Sarcomas in 62 Patients***

Location	No. (%) of patients
Antrum or lesser curvature or both	43 (69)
Antrum, lesser curvature, body, + or – cardia	8 (13)
Antrum, body, cardia	2 (3)
Other combinations of locations	9 (15)

*+ = present; – = absent.

Extra-adrenal Paraganglioma

Thirty-seven patients (47%), ranging in age from 12 to 48 years (mean, 27.5 years; median, 27 years), had 60 paragangliomas (Table 4). Diagnosis was based on histological findings in 34 patients (92%) and on clinical, biochemical, and radiographic findings in 3 patients (8%). The latest age at discovery of a new paraganglioma (among patients who had multiple such tumors) was 61 years. Multiple sites (up to 5) were affected in 8 patients (22%). Six patients (16%) had pheochromocytoma. Metastasis occurred in 4 patients (10%).

Symptoms, Signs, and Laboratory and Radiographic Findings.—Manifestations included symptoms and signs of catecholamine excess associated with increased urinary content of catecholamines and their metabolites in 13 patients, symptomatic masses in 10 patients, or asymptomatic masses (neck, mediastinal, or abdominal) in 14 patients. Lesions were localized by radiography, angiography, computed tomography, and radioactive iodine–metaiodobenzylguanidine (^{131}I MIBG) scintiscanning.

Table 4. **Site of Origin of 60 Paragangliomas in 34 Patients***

Tumor site and type	No. of tumors
Head and neck	
Glomus tympanicum	5
Glomus jugulare	2
Glomus vagale	2
Carotid body	8†
Larynx	2
Thyroid	1
Chest	
Superior mediastinum	3
Aortopulmonary body	9
Sympathetic chain	2
Abdomen	
Retroperitoneum (5 para-adrenal)	7
Adrenal	6‡
Sympathetic chain	9
Organ of Zuckerkandl	2
Liver, porta hepatis	2

*Diagnosis on clinical, biochemical, and radiographic findings in 3 other patients.
†Bilateral in 1 patient.
‡Three had extra-adrenal paragangliomas also.

Surgery and Other Treatment.—Thirty-one patients had 40 operations (1 patient had 5 procedures) for complete or incomplete removal of 50 separately located paragangliomas. Five patients underwent adrenalectomy (bilateral in 1). Inoperable tumors in 5 patients were treated with phenoxybenzamine hydrochloride, chemotherapy, radiation, or polyvinyl alcohol particle embolization. One patient with bilateral adrenal ^{131}I MIBG positivity and normal results of catecholamine studies remained under study.

Pathological Findings.—The tumors were firm and had a fleshy-appearing cut surface. The cells displayed eosinophilic to clear granular cytoplasm and were arranged in a trabeculoalveolar pattern supported by a fibrovascular stroma.

Results of Surgery.—Forty-five paragangliomas were cured for 3 to 20 years (mean, 12 years; median, 8 years). Two patients each had secondary surgery for recurrent carotid body paraganglioma and incompletely excised aortopulmonary paraganglioma; 1 patient had reoperation for laryngeal paraganglioma and 3 operations for vertebral metastasis.

Follow-up

Follow-up was obtained in the 79 patients (100%), to death or to September 1997 or later. The period ranged from 1 year to 49 years (mean, 20.6 years; median, 20 years) and exceeded 30 years in 15 patients. Sixty-four patients (81%) were alive, 19 (30%) without residual tumor, for 5 to 44 years (mean, 19 years; median, 16 years) after onset. The oldest survivor was 60 years old.

Forty-eight patients (61%) were alive with residual or metastatic tumors. Twenty-one patients (27%) were alive with hepatic metastatic sarcoma for 1 year to 25 years (mean, 9.3 years; median, 7 years); 4 also had recurrent gastric sarcoma, considered to have been inoperable in 2 for 12 and 15 years (Table 5). Metastatic tumors grew slowly, frequently became cystic, and were unaffected by systemic chemotherapy, radiotherapy, or hyperthermia. Hepatic metastatic lesions decreased in size spontaneously in 2 patients, following a high fever in 1, and increased by 10% during pregnancy in 1 patient. Five patients were alive, having had peritoneal spread for 1 year to 30 years (mean, 10.6 years; median, 10 years); 2 also had hepatic metastases for 5 to 16 years.

Twenty-six patients were alive with pulmonary chondromas, 9 of whom had other components of the triad. Five chondromas were excised from 1 patient's left lung at age 25 years[1]; 22 years later, she had 12 calcified nodules in her left and right lungs. (She also had radiographic evidence of

Table 5. **Tumors Present at Last Follow-up in 45 of 64 Living Patients***

Recurrent gastric sarcoma	Metastatic gastric sarcoma		Pulmonary chondroma	Paraganglioma	No. of patients
	Liver	Peritoneum			
+	+		+	+	1
+	+				3†
	+	+	+		1
	+	+			1
	+		+		5
	+				9‡
	+			+	1
		+	+		1
		+		+	1
		+			1
			+	+	1
				+	3§
			+		17

*+ = present.
†One also had unresected adrenal mass.
‡One also had bilateral adrenal ^{131}I MIBG–positive tumors.
§One with metastasis.

recurrent and hepatic metastatic gastric sarcoma and a 2.6-cm, nonfunctioning, ^{131}I MIBG–negative adrenal mass.) Another patient had a normal chest radiograph at the age of 18 years; 7 years later, 3 calcified lung lesions were found; another lesion developed between the ages of 25 and 27 years; at 28 years, there were 5 calcified tumors (3 on the right and 2 on the left); and 3 additional nodules were present at the age of 37 years. One patient whose lung lesions were initially detected at the age of 27 years[38] had at least 6 calcified pulmonary nodules (the largest 10 cm in diameter) at the time of his death at the age of 67 years due to hepatic metastatic sarcoma. In general, the chondromas exhibited slow growth or became stable.

Seven patients were alive with paraganglioma (metastatic in 1). Four additionally had combinations of residual gastric sarcoma, metastatic gastric sarcoma, and pulmonary chondroma. One patient presumed to have hepatic metastatic paraganglioma on the basis of positive findings on ^{131}I MIBG scintiscan did not have paraganglioma elsewhere.

Fifteen patients (19%) were dead, 10 (13%) of the disorder, 3 of other causes but with elements of the triad present, and 2 of causes presumably unrelated to the triad (Table 6). Pulmonary metastatic gastric carcinoma contributed to the death of 1 patient with hepatic metastatic sarcoma.[56] The disorder had been present in the group for a mean of 19.6 years (median, 18 years).

Family

Status information was available for 118 parents, 103 children, and 136 siblings of the patients. A sibling of each of 2 patients with gastric sarcoma and paraganglioma had bilateral carotid body paragangliomas. One of the siblings also had asymptomatic bilateral adrenal masses that were interpreted radiologically as nonfunctioning adenomas (urinary content of catecholamines and their metabolites was normal; ^{131}I MIBG scanning had not been performed).

DISCUSSION

This study provides insight into the natural history of an unusual disorder, the triad of gastric stromal sarcoma, pulmonary chondroma, and paraganglioma, and shows that it is chronic, persistent, and indolent. Thus far, only 10 patients (13%) have died of causes directly attributable to the disorder, but it contributed to the deaths of 2 others, and the number of deaths doubtless will increase because 28 surviving patients (35%) have inoperable or metastatic gastric stromal sarcoma or residual or metastatic paraganglioma. Most of patients had only 2 of the 3 components. Long follow-up was required in some cases to observe development of the second component, in 1 instance 26 years. Presumably, some patients with the triad trait never manifest a second component.

Key features of the gastric tumors were (1) early occurrence, (2) few local symptoms, (3) intramural origin with eventual mucosal ulceration and serosal involvement, (4) predilection for the antrum and lesser curvature, (5) multifocal occurrence with propensity for local recurrence, (6) widespread intra-abdominal metastasis, by lymphovascular and transcoelomic routes and infrequent extra-abdominal spread, (7) very slow progression of metastasis, and (8) resistance of metastatic lesions to adjuvant therapy.

Table 6. **Cause of Death Among 15 Patients With the Triad**

Cause of death	Metastatic sites	Age (y)	Years after onset
Dead of disease			
Residual and metastatic gastric sarcoma	Liver, forearm (skeletal muscle)	31	18
Residual and metastatic gastric sarcoma	Liver, peritoneum	34*	20
Vagal body paraganglioma	…	35	12
Metastatic paraganglioma	Bone (vertebra, femur)	36	7
Metastatic gastric sarcoma	Liver, peritoneum	39	16
Recurrent aortopulmonary paraganglioma	…	40	22
Metastatic gastric sarcoma and paraganglioma	Liver, pleura, bone (ribs, pelvis)	41	25
Metastatic gastric sarcoma and metastatic gastric carcinoma	…	51	40
Paraganglioma, site undetermined	…	59	33
Metastatic gastric sarcoma	Liver	69	48
Dead of other cause (with disease)			
Postoperative complications (unresected gastric sarcoma)	…	40	0
Metastatic abdominal adenocarcinoma, primary unknown	Peritoneum	43	24
Postoperative complications (metastatic gastric sarcoma)	Liver, peritoneum	48†	5
Subarachnoid hemorrhage (metastatic gastric sarcoma)	Liver	51	5
Lung carcinoma (pulmonary chondroma)	…	53	19

*Partial resection of primary tumor only.
†Patient had had calcified lung lesions since the age of 18 years that were never biopsied.

Initially, the sarcomas were thought to arise from smooth muscle (hence, the terms "leiomyoblastoma" and "epithelioid leiomyosarcoma"[4]). Because smooth muscle markers could not be consistently identified in them, they are now referred to as "gastric stromal sarcomas." Certain of their ultrastructural features (interdigitating cell processes and dense-core granules) and immunocytochemical properties (c-*kit* positivity) suggest neural differentiation. The tumors may originate from precursors of the interstitial cells of Cajal.[47,62]

Features of the pulmonary tumors were (1) early appearance, (2) absence of symptoms, (3) absence of deleterious effects, (4) multifocal, bilateral, and peripheral occurrence, (5) coarse, often peripheral calcification, (6) benign behavior, (7) cure by surgery, and (8) propensity for development of new tumors. The chondromas were mesenchymal neoplasms, not featuring the epithelium-lined clefts characteristic of pulmonary hamartoma, the lesion with which they were commonly confused pathologically (and radiologically).

Paraganglioma characteristics included (1) occurrence at a young age, (2) extra-adrenal location, with unusual sites affected (aortopulmonary body, larynx, thyroid, and possibly liver), (3) multifocality, (4) catecholamine secretion, (5) benign behavior usually, and (6) amenability to surgical cure (location dependent) and control by other means when inoperable.

The unmodified natural history of the triad was not observed, because manifestations of 2 components, the gastric sarcoma and the paraganglioma, eventually required surgical intervention. The gastric tumors were usually large at discovery. Judging by the slow growth of metastatic lesions, the primary tumors were probably present for many years before detection. In 1 patient,[24] gastric surgery at the age of 20 years was preceded by intermittent epigastric pain and recurrent melena for 10 years. A patient[7] with inoperable gastric sarcoma at the age of 18 years was treated with radiotherapy. Reoperation at 25 years for persisting anemia showed massive hepatic and peritoneal metastatic spread. She died of gastric hemorrhage at the age of 35 years. The findings suggest that the gastric tumors begin to develop in the first decade of life and, if left untreated, are fatal as the result of gastric hemorrhage rather than metastasis. The natural history of the paragangliomas has similarly been terminated or altered in most cases by surgical intervention, which is usually curative. The long-term outlook for inoperable tumors responding to combinations of radiation, chemotherapy, and embolization is unpredictable. A few pulmonary chondromas left in situ and observed for up to 40 years have

remained asymptomatic and have not caused deleterious effects.

Ten patients (13%) had adrenocortical tumors. Four others each had unresected adrenal tumors, including 1 with bilateral adrenal ^{131}I MIBG positivity. The adrenal lesions were sometimes multifocal and occasionally bilateral—the pattern of adrenal tumoral syndromic involvement. Such findings are unlikely to be happenstance, especially since adrenal nodules, even microscopic ones, are unusual in the first 3 decades of life.[63] They justify acceptance of adrenocortical tumors as a component of the triad. Prior knowledge of this additional association resulted in a tentative diagnosis of the disorder in a 25-year-old Mayo Clinic patient with recurrent gastric stromal sarcomas and a 4-cm nonfunctioning adrenal mass that had been interpreted clinically as a cortical adenoma. This diagnosis was confirmed at surgery; importantly, a nonfunctioning paraaortic paraganglioma was also found, establishing the diagnosis of the triad.

Intramural esophageal tumors and duodenal and proximal small intestinal tumors occurred in 7 and 8 patients, respectively. Most were histologically similar to the gastric stromal tumors, but a few of the esophageal neoplasms were leiomyomas, which merit consideration as a component of the triad. However, a precursor cell might exist with potential to differentiate along neural and smooth muscle routes, providing a possible explanation for the stromal sarcomas and the leiomyomas. If this were the case, occasional gastric tumors might prove to be leiomyomas or leiomyosarcomas rather than stromal sarcomas. (It is not logical to refer to a condition comprising 4 and possibly 5 conditions as a "triad"; this is done because of prior usage of the designation "Carney's triad"[2,20,23,27,30,31,34-38] and because the condition is referred to as the Carney triad in McKusick's *Mendelian Inheritance in Man*[64].)

The occurrence of paragangliomas in a sibling of each of 2 unrelated patients, both of whom had gastric sarcomas and paragangliomas, also seems unlikely by chance. Components of the triad had not occurred in 355 of the primary relatives (parents, siblings, and children) of affected patients. The pattern of paraganglioma, bilateral and multifocal, in the 4 patients is that of familial paraganglioma.[64] Therefore, the 2 sibships might have been exhibiting familial paraganglioma with either coincidental or specific occurrence of gastric stromal sarcomas in both. These explanations are not satisfying. Gastric stromal sarcoma has not occurred in 549 patients (290 males and 259 females) from 115 kindreds with familial paraganglioma,[65-143] and the likelihood of multiple gastric stromal sarcomas and multiple paragangliomas occurring by chance in more than 1 patient seems remote. Therefore, the possibility that the triad might be familial must be considered. Familial occurrence (male predominance) of gastrointestinal stromal tumors, mast cell disease, and perineal hyperpigmentation has been reported[144,145]; neither of the latter 2 conditions was described among patients with the triad.

Guidelines for the diagnostic evaluation, management, and treatment of patients with the triad are available.[2] A few supplemental comments based on the findings in this study will be made. Despite the propensity for additional gastric tumors to develop in the remaining stomach, less than total gastrectomy, if feasible, is probably the best initial operation to avoid the complications of total gastrectomy, particularly in teenaged patients. Patients treated in this manner should be advised that new gastric tumors may develop and be reexamined at 3-year intervals indefinitely. For hepatic metastatic lesions of the gastric sarcomas, those that are accessible can reasonably be excised; those that are inaccessible may be amenable to chemoembolization, cryoablation, thermoablation, or a combination of these techniques; and those that produce symptoms after tumor degeneration and fluid accumulation might benefit from aspiration. Evaluation of adrenal tumors in patients with gastric stromal sarcomas or pulmonary chondromas (or both) should include study of cortical as well as medullary function. A family history should be elicited from patients with the triad and those suspected of having it (1 component of the disorder only), with attention to its components and other conditions in the family. At this time, family screening and genetic counseling for the disorder are not warranted. Lookout should be maintained for the occurrence of gastric stromal sarcomas or pulmonary chondromas in kindreds with familial paraganglioma.

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