Synchronous Occurrence of Epithelial and Stromal Tumors in the Stomach

A Report of 6 Cases

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• ***Objective.*—The synchronous development of epithelial and stromal tumors in the stomach has been reported rarely in the literature. A series of 6 such cases is described in this article.**

***Methods.*—Clinical and pathologic data were recorded and the literature was reviewed.**

***Results.*—Five cases featured the simultaneous occurrence of stromal tumors (1 benign, 3 borderline, 1 malignant) and adenocarcinomas, whereas the stromal tumor in the sixth case was found in association with a carcinoid. No collision tumors were observed. In 2 cases, tumors arose from the same site and were closely juxtaposed, but in 4 patients they developed from different areas of the stomach. A preoperative histologic diagnosis of both tumors was not achieved in any case. Two patients harbored occult infiltrative epithelial lesions (1 diffuse-type adenocarcinoma, 1 carcinoid), which were detected only at pathologic examination of the gastric mucosa adjacent to the stromal tumor.**

***Conclusions.*—The simultaneous occurrence of epithelial and stromal tumors in the stomach can be less rare than usually expected. Coincidence alone could account for such an association, particularly in areas with high incidence rates of gastric cancer. The hypothesis that a single carcinogenic agent might interact with two neighboring tissues in the stomach inducing the development of tumors of different histotype cannot be theoretically discarded.**

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In recent years, the synchronous occurrence of tumors of different histotypes arising in the same organ has been reported more frequently in the literature. In the stomach, adenocarcinoma has been described with coexisting primary rhabdomyosarcoma,[1] carcinoid,[2] and low-grade B-cell lymphoma of mucosa-associated lymphoid tissue.[3,4] The simultaneous development of gastric mesenchymal tumor and adenocarcinoma has been documented rarely. A search of the literature uncovered approximately 30 cases of coexistent adenocarcinoma and leiomyoma or leiomyosarcoma in the stomach, the majority of which were reported in the Japanese literature.[5–12] These cases have been documented as single case reports, and the largest study comprised 2 cases.[7]

In this article, we describe 5 cases of synchronous occurrence of stromal tumors and adenocarcinomas in the stomach. In a sixth case, the simultaneous association of gastric stromal tumor (GST) and carcinoid was observed.

MATERIALS AND METHODS

Cases of synchronous gastric epithelial and stromal tumors were retrieved from the files of the Institute of Pathological Anatomy of the University of Modena (Modena, Italy) during the years 1988 through 1997. In a 10-year review, we were able to uncover 2035 cases of gastric epithelial tumors (2010 adenocarcinomas, 25 carcinoids) and 52 GSTs. The synchronous occurrence of adenocarcinoma and stromal tumor was observed in 5 cases, whereas in 1 case the stromal tumor was found in association with carcinoid. Clinical records and pathologic reports were reviewed in each case.

Specimens had been fixed in 4% formaldehyde and embedded in paraplast. Sections were stained with hematoxylin-eosin. Gastric carcinomas were classified according to Lauren's criteria.[13] Stromal tumors were categorized as benign (<5 mitoses/50 high-power fields [hpf]; size <5 cm), borderline (<5 mitoses/50 hpf; size >5 cm), and malignant (>5 mitoses/50 hpf).[14] Based on the predominant pattern, the lesions were further subdivided as spindle or epithelioid-type stromal tumors.[14]

Clinical outcome and family history of cancer were evaluated by consulting clinical charts, individual pathology files, and death certificates. In some cases, the patient or close relatives and the family doctor were interviewed.

Immunohistochemistry was performed in all stromal tumors using the streptavidin-biotin amplification system and a panel of commercially available antibodies directed against the following antigens: vimentin (monoclonal; Dakopatts A/S, Glostrup, Denmark), desmin (monoclonal; Eurodiagnostica BV, Arnhem, The Netherlands), muscle-specific actin (monoclonal, clone HHF35; BioGenex, San Ramon, Calif), S100 protein (polyclonal; Bio-Optica, Milan, Italy), and CD34 (monoclonal, clone QB-END-10; Ylem, Rome, Italy).

RESULTS

Case Histories

The clinical features of patients are summarized in Table 1. Patients included 3 men and 3 women, whose ages ranged from 69 to 81 years. Patients had sought medical

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Table 1. Clinical Features of Patients*					
Case No.	Sex/Age, y	Preoperative Diagnosis	Family History of Cancer	Surgical Treatment	Status at Follow-up (mo)
1	F/81	Adenocarcinoma	NA	PG	DUC (21)
2	F/79	Pyloric stenosis	Negative	PG	ANED (54)
3	M/75	Adenocarcinoma	Positive	TG	ANED (12)
4	F/79	Adenocarcinoma	Negative	TG	ANED (28)
5	M/79	Adenocarcinoma	Negative	TG	ANED (75)
6	M/69	Suspected GST	Negative	Removal of submucosal nodule	DUC (12)

* GST indicates gastric stromal tumor; NA, not assessed; PG, partial gastrectomy; TG, total gastrectomy; DUC, dead, unrelated causes, and ANED, alive, no evidence of disease.

advice because of such vague symptoms as epigastric pain, nausea, or abdominal discomfort. Esophagogastroduodenoscopy showed an ulcer or a polypoid mass in the stomach. The endoscopic finding was suspicious for GST in case 6. On small biopsy fragments, a pathologic diagnosis of adenocarcinoma was rendered in cases 1, 3, 4, and 5, whereas normal gastric mucosa was detected in case 6. Pyloric stenosis was detected at radiographic examination in case 2, but endoscopy could not be performed because of the patient's intolerance. A preoperative histologic diagnosis of both neoplasms was not achieved in any case. Partial or total gastrectomy was performed in all patients, except in patient 6, who underwent removal of a submucosal nodule covered by apparently normal mucosa.

Family history of cancer was assessed in 5 patients and turned out to be negative in 4. A strong cancer aggregation was found in patient 3. A sister and a brother of this patient had died of gastric cancer at 58 and 60 years of age, respectively, whereas another brother had died of colon cancer at 70 years, and a living sister had been operated on for gastric carcinoma at 55 years of age. Coexisting gastrointestinal stromal tumors were not reported.

Four patients are still alive with no evidence of recurring disease or distant metastases after follow-up periods ranging from 12 to 75 months, whereas the remaining 2 patients (cases 1 and 6) died of unrelated causes (cerebral hemorrhage and heart attack) 12 and 21 months after surgery, respectively. In these 2 patients, abdominal computed tomographic scans and thoracic radiographs performed a few months before death had disclosed no metastatic deposits.

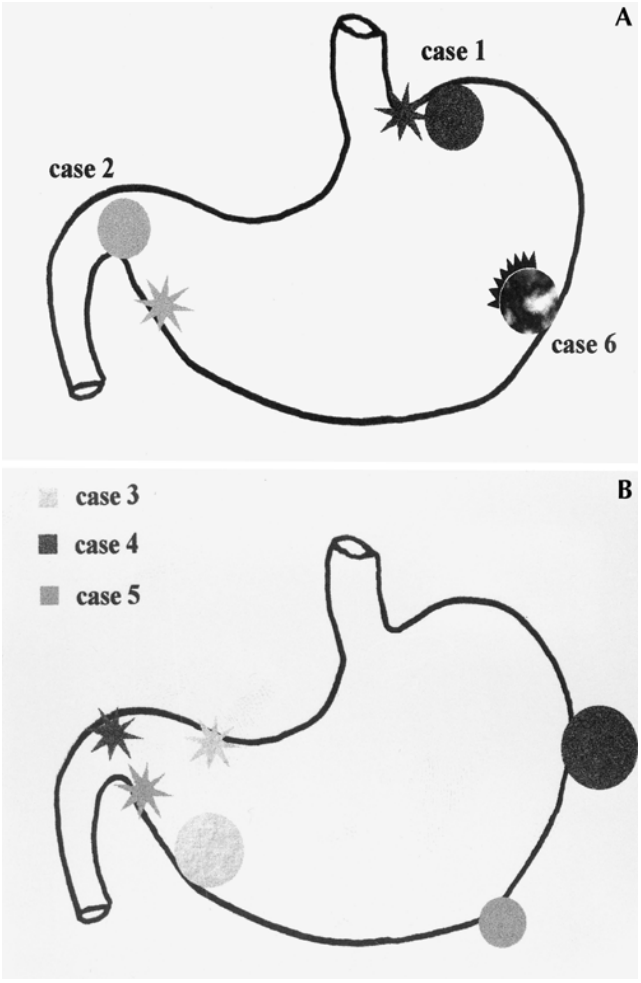

Figure 1. *A, Localization of cases 1, 2, and 6 in the stomach. Circle indicates gastric stromal tumor; star, adenocarcinoma; and crown, carcinoid. B, Localization of cases 3, 4, and 5 in the stomach. Circle indicates gastric stromal tumor; star, adenocarcinoma.*

Pathologic Findings

In cases 1 and 6, a single mass was detected at macroscopic examination (Figure 1, A). At histology, a well-differentiated adenocarcinoma and an epithelioid stromal tumor were diagnosed in case 1. Although closely juxtaposed, the 2 neoplasms did not merge to form a collision tumor, but were separated by a thin rim of residual, normal-looking muscularis propria (Figure 2). Case 6 featured a 5 × 3-cm submucosal nodule, which had been resected together with a rim of surrounding gastric wall. Histologic examination disclosed a borderline stromal tumor. The overlying mucosa harbored a 0.6-cm focus of carcinoid, which invaded the lamina propria and initially infiltrated the submucosa (Figure 3).

In the 4 remaining patients (cases 2 through 5), 2 distinct lesions separated by nonneoplastic gastric wall were grossly recognizable (Figure 1). Case 2 featured an ulcerated adenocarcinoma of the antrum, which was located 4 cm proximally to a 6 × 2-cm pyloric submucosal stromal tumor. In case 3, the 2 neoplasms were located in separate areas of the antrum (adenocarcinoma in the lesser curvature, stromal tumor in the greater curvature), whereas in cases 4 and 5 they arose from different regions of the stomach (pylorus and body, antrum and body, respectively).

Adenocarcinomas had the gross appearance of an exophytic polypoid mass or ulcer (Table 2). Four cases were

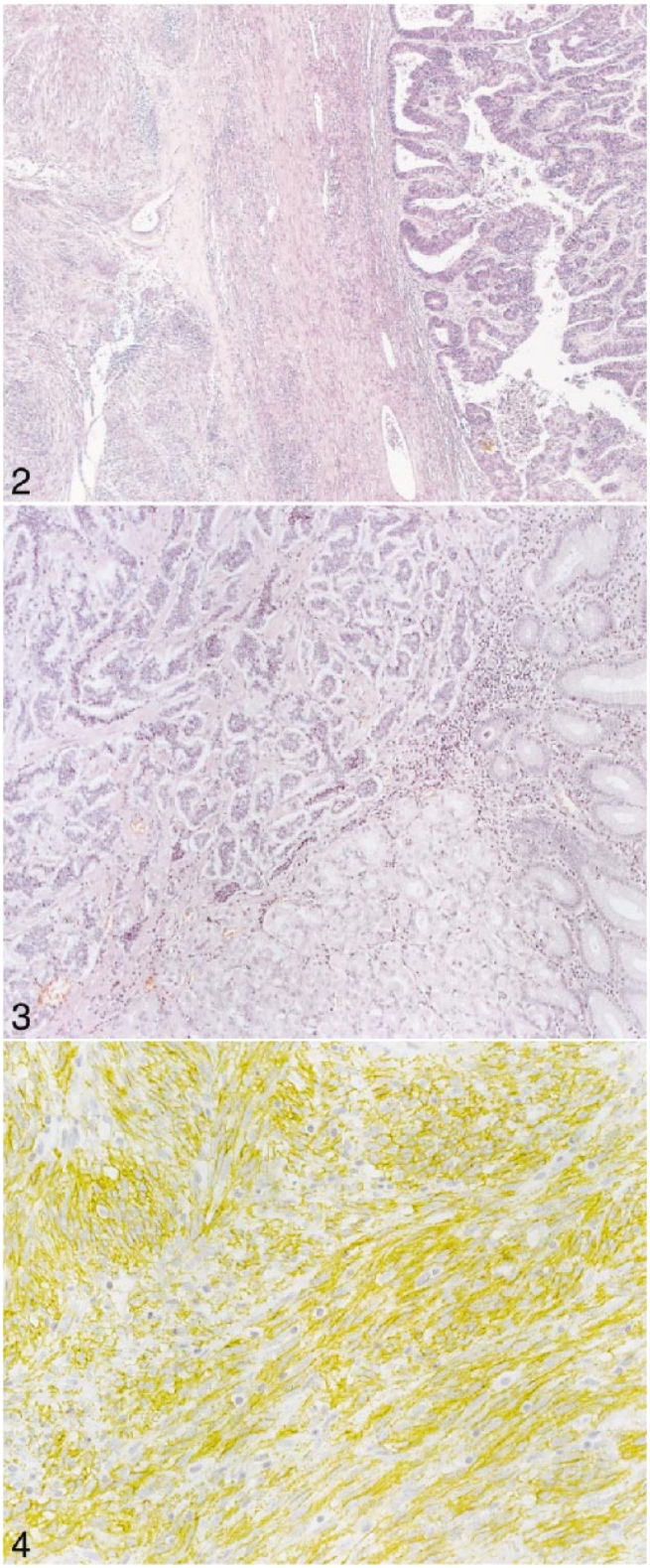

Figure 2. *Case 1. Well-differentiated adenocarcinoma and stromal tumor separated by residual normal gastric wall (hematoxylin-eosin, original magnification ×120).*

Figure 3. *Small mucosal carcinoid (hematoxylin-eosin, original magnification ×180).*

Figure 4. *Case 4. Positive immunohistochemical reaction for CD34 in stromal tumor (streptavidin-biotin, original magnification ×240).*

intestinal-type adenocarcinomas, and 1 was diffuse-type. Tumors infiltrated the submucosa or invaded the muscularis propria. In case 1, the neoplasia penetrated the subserosa but did not reach the visceral peritoneum.

Gastric stromal tumors (Table 3) were composed of spindle cells, with the exception of case 1, which featured epithelioid cells. Three of these tumors were submucosal, whereas 2 developed in a subserosal location and 1 was an intramural mass. Applying previously outlined criteria,[14] 1 tumor was classified as benign, 4 as borderline, and 1 as malignant (Table 3).

All stromal tumors stained strongly and diffusely with antibody to vimentin, whereas 4 of the tumors (cases 2, 4, 5, and 6) showed reaction with the CD34 antibody (Figure 4), and 2 were focally positive for S100 protein (cases 1 and 3). None of the cases stained with antibodies to either desmin or muscle-specific actin.

The nonneoplastic gastric mucosa showed inflammatory lesions in some patients. Chronic gastritis with multifocal atrophy was detected in 2 cases (patients 2 and 3), whereas in cases 4 and 5 antrum-predominant active chronic gastritis was observed. *Helicobacter pylori* infection was found in patients 2, 3, and 4. Foci of complete (type I) intestinal metaplasia were observed in cases 2 and 3. Gastric dysplasia was not detected in any of the patients.

COMMENT

The simultaneous development of epithelial and stromal tumors in the stomach has been reported rarely in the literature. So far, such an association has been documented in single case reports that outline the occurrence of adenocarcinoma together with gastric leiomyoma[8,12,15] or leiomyosarcoma.[5,7,10,11,16] Carcinoid has been found in association with leiomyoma[17] and carcinosarcoma.[18] The majority of previously reported tumors were located in different regions of the stomach, although isolated cases of collision tumors also have been observed.[6,9] Adenocarcinomas were usually of intestinal type[13] and invaded the gastric wall, but at times they were confined to the mucosa or, at most, infiltrated the submucosa.[5,7] Currently, the noncommittal term *gastric stromal tumor,* originally coined by Mazur and Clark,[19] is usually employed to designate neoplasms previously defined as leiomyoma or leiomyosarcoma.

The synchronous gastric tumors described in this report occurred as independent primaries. Neither the intimate mixing of different histogenetic elements typical of so-called gastric adenocarcinoleiomyosarcoma,[20] nor the intermingling of morphologically distinct entities, usually observed in collision tumors, were detected. In 4 cases, tumors developed from different areas of the stomach, whereas in the remaining 2 cases they arose from the same site but did not merge. In our series, 6 of 2035 stomachs with epithelial tumors (adenocarcinoma or carcinoid) harbored a synchronous stromal tumor (frequency of association, 0.29%). In 4 of these cases, adenocarcinoma was diagnosed preoperatively on biopsy fragments and the GST was found incidentally at surgery, whereas in 2 patients (cases 2 and 6) surgery was performed either because of pyloric stenosis or suspected submucosal GST, and the coexistent epithelial lesions (1 diffuse-type adenocarcinoma, 1 carcinoid) were detected only at pathologic examination.

The simultaneous finding of epithelial and stromal gastric tumors raises the question of whether such an occur-

Table 2. Pathologic Features of Gastric Epithelial Tumors					
Case No.	Site	Size, cm	Gross Appearance	Histology	Stage (pTNM)
1	Cardias	4.0	Vegetant mass	Adenocarcinoma, intestinal type	T2b N0 M0
2	Antrum (4 cm proximal to pylorus)	2.0	Erosion	Adenocarcinoma, diffuse type	T1b N0 M0
3	Antrum	4.0	Ulcer	Adenocarcinoma, intestinal type	T2a N1 M0
4	Pylorus	1.2	Ulcer	Adenocarcinoma, intestinal type	T2a N1 M0
5	Antrum	2.0	Ulcer	Adenocarcinoma, intestinal type	T2a N0 M0
6	Corpus	0.6	Sessile polyp	Carcinoid	T1b NX MX

Table 3. Pathologic Features of Gastric Stromal Tumors				
Case No.	Site	Size, cm	Gross Appearance	Histology
1	Fundus	5.0	Intramural mass	Epithelioid borderline
2	Pylorus	6 × 2	Submucosal mass	Spindle cell malignant
3	Antrum	5.0	Submucosal nodule, sessile	Spindle cell borderline
4	Corpus	5 × 3	Subserosal nodule	Spindle cell borderline
5	Corpus	0.6	Subserosal nodule	Spindle cell benign
6	Corpus	5 × 3	Submucosal nodule	Spindle cell borderline

rence is a simple incidental association or the 2 lesions are connected by a causal relationship. The suggestion that the stomach harboring a leiomyosarcoma may have a tendency to develop malignant epithelial lesions was put forward by Tada et al in 1984.[7] It is difficult to conceive, however, how a stromal tumor might exert a favorable influence on the development of a nearby epithelial neoplasm. Among the pathologic processes known to be associated with increased risk of adenocarcinoma,[21] only atrophic gastritis and *H pylori* infection were observed in some of the patients in this series. Stenosis is not a risk factor for gastric cancer.[21] Coincidence alone could easily account for such an association, particularly in areas that exhibit high incidence rates of gastric cancer, such as Japan. Of interest, our study was carried out in Northern Italy (Modena Province), where crude incidence rates of stomach cancer are moderately high (37/100 000 in men and 28/100 000 in women).[22]

The possibility that gene mutations might underlie tumor predisposition in patients harboring a double gastric neoplasia cannot be theoretically discarded. At present, however, no data are available to support such a hypothesis. In our cases, family histories of 5 patients were screened accurately, but evidence of familial disease was derived in 1 case only.

An interesting hypothesis is that a single carcinogenic agent might interact with 2 neighboring tissues, inducing the development of tumors of different histotypes in the same organ. Experimental evidence for this possibility has been provided. *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine induces the development of gastric adenocarcinomas after oral administration in rats.[23] However, when the same compound is combined with agents that alter the gastric mucosal barrier, such as aspirin or stress, leiomyosarcomas develop in conjunction with epithelial tumors.[24] Equally compelling, although also experimental, are reports on the induction of gastric tumors in rats after 9,10-dimethyl-1,2-benzanthracene (DMBA) injection. Whereas administration of DMBA alone induces the development of adenocarcinomas, treatment with DMBA and cellophane plate causes mainly the induction of gastric sarcomas.[25]

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