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CASE REPORT

Composite (Adenocarcinoid) Tumors of the Gastrointestinal Tract

HULYA LEVENDOGLU, MD, FACG, CONRAD A. COX, MD, and VENKAT NADIMPALLI, MD

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In recent years, it has become known that carcinoid tumors show a much wider spectrum than was originally thought. A variety of histologic presentations including glandular differentiation, mucin production, spindle cell configuration, and even osseous or squamous metaplasia have been reported in carcinoid tumors (1, 2). In addition, adenocarcinomas of the gastrointestinal tract were reported to contain both epithelial and endocrine cells (3). In instances where endocrine cells comprised a significant proportion of the tumor, the terminology of "adenoendocrine cell carcinomas" has been used (4). In the spectrum of carcinoid to carcinoma, there also is a group of tumors that contain carcinoid tissue in one area of the tumor and adenocarcinoma in the other, although these two different histologic patterns are not individually intermixed. These tumors have been named composite or collision tumors (5–28). Lewin, however, in his classification of mixed endocrine cell tumors uses the term "composite" where both the endocrine and epithelial cells are intermixed within the same tumor tissue and reserves the term "collision" for tumors where two different histologic patterns are in intimate contact without the intermixture of individual cell types (4). However, this type of classification gives more credit to the hypothesis that collision tumors coincidentally arise next to one another and are not true single neoplasms which differentiated in two directions (15). Since the common or different cell origin is still not very clear, we will use the term composite tumor in our description of six cases where two histologically different tissues were found in juxtaposition to each other in the same tumor tissue removed by surgery.

Composite tumors are rare; all cases involving gastrointestinal tract have been described in the literature as isolated case reports (5–28). Although, appendiceal composite tumors are well characterized both clinically and histologically, (6–14), clinical data and the course of patients with composite tumors from the other parts of the gastrointestinal tract were not described in detail as opposed to a better documentation of the histology of these tumors. We herewith report six patient with composite tumors with detailed information on the clinical course and outcome of these patients as well as the histologic evaluation of the tumor tissue. In this context, we also reviewed the available information in the literature to further characterize this variant of carcinoid tumor clinically. We believe that better description and identification of these tumors may lead to a recognition of distinct clinical behavior between carcinoid and carcinoma and may have an alternative therapy in the future according to their location in the gastrointestinal tract.

CASE REPORTS

We diagnosed six patients since 1984 at Cook County Hospital with composite tumors. The tissues had been fixed in 10% buffered formalin and paraffin embedded in a routine manner. The microscopic sections were examined with hematoxylin and eosin (H&E), mucicarmine for mucin production, modified Grimelius for argyrophil reaction, and with Fontana stains for argentaffin reaction. The tumors in H&E-stained sections showed the characteristics of adenocarcinoma with well-defined glandular formation in some areas, sheets of uniform neoplastic cells in other areas forming solid cords or nests, or

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From the Division of Gastroenterology and Surgical Pathology, Cook County Hospital, Hektoen Institute for Medical Research and Rush University Medical Center, Chicago, Illinois.

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Address for reprints requests: Dr. Hulya Levendoglu, Division of Gastroenterology, The Brookdale Hospital Medical Center, Linden Blvd at Brookdale Plaza, Brooklyn, New York 11212.

TABLE 1. CLINICAL DATA IN SIX PATIENTS WITH COMPOSITE TUMORS

Age (years)	
Range	41–68
Mean	58
Sex (male/female)	5:1
Symptoms (No. of patients)	
Abdominal pain	5
Anorexia	5
Weight Loss	4
Nausea/vomiting	2
Hematemesis	1
Melena	1
Change in bowel habits	5
Physical findings	
Abdominal tenderness	3
Abdominal mass	3
Guiac + stool	5
Bowel obstruction	2

forming trabecula or anastomosing in ribbonlike cords in richly vascularized stroma. The tissues from these patients subsequently were submitted for electron microscopic (EM) studies to confirm endocrine and nonendocrine cell features. Although EM was performed on deparaffinized tissue, satisfactory pictures were obtained in all of these patients.

RESULTS

Clinical Findings. There were only five males and one female with ages ranging from 41 to 68 years (mean age: 58 years) (Table 1). Symptoms and physical findings in all were suggestive of a malignancy in the gastrointestinal tract with a palpable abdominal mass in half of them (Table 1). Two patients presented with bowel obstruction. Anemia with hemoglobin value less than 10 g/dl was present in four and leukocytosis of more than 10,000 cells/mm^3 in two patients. Tumor was localized in the colon in three, proximal jejunum in two, and in the stomach in one patient. Operative findings, extension of tumor, and the outcome of these patients are presented in Table 2. Tumor size ranged from 4 to 10 cm. Serosal and lymph node metastasis and a larger tumor size were associated with poor prognosis. Two patients with largest tumor diameter of 10 cm, lymph node metastasis, and serosal extension of tumor died three and nine months after operation.

Histopathologic Findings. Tumor was discretely separated into carcinoid and carcinomatous parts. In no specimen were the carcinoid-type cells scattered among adenocarcinoma cells. Tumor showed extensive ulcerations on the surface in all patients. The adenocarcinoma part in all was moderately differentiated (Figure 1A). There were numerous mitoses in the glands in all patients. In one patient abundant extracellular mucin production was seen in the tumor arising from the cecum (patient 5). In the carcinoid areas, the tumor was composed of solid nests of uniform small cells with large hyperchromatic oval nuclei forming trabeculae or interanastomosing bands with focal rosettelike formations or simply showed solid groupings (Figure 1B). Extensive fibrosis was present in the vicinity of the tumor in two patients (patients 3 and 4). Argentaffin reaction was demonstrated in some cells in patients with tumors arising from cecum and rectum (patients 4 and 6). Lymph node metastasis were histologically adenocarcinoma in two patients (patients 1 and 4) and carcinoid in one patient (patient 5).

TABLE 2. CHARACTERISTICS OF TUMOR AT OPERATION AND OUTCOME IN SIX PATIENTS WITH COMPOSITE TUMORS

Patient	*Location of tumor*	*Size of tumor (cm)*	*Extension of tumor*	*Type of operation*	*Outcome/postsurgery*
1	Stomach	4 × 3 × 1	Muscular wall and subserosa. 1/14 lymph nodes positive	Radical subtotal gastrectomy	Alive/36 months
2	Proximal jejunum	9 × 8 × 1.5	Deep muscular wall 0/19 lymph nodes positive	Resection of jejunal segment	Alive/39 months
3	Proximal jejunum	9 × 9 × 5.5	Serosa	Resection of jejunal segment	Alive/10 months
4	Cecum	10 × 3 × 2	Periocolic fat, peritoneum, liver diaphragm. 16/21 lymph nodes positive	Right hemicolectomy ileal resection	Dead/3 months
5	Cecum	9 × 10 × 1.3	Serosa. Several matted mesenteric lymph nodes positive	Subtotal colectomy	Dead/9 months
6	Rectum	6 × 4 × 3	Pericolic fat, liver peripancreatic lymph nodes by CT. 0/2 removed lymph nodes positive	Sigmoid resection, low anterior anastomosis	Alive/8 months

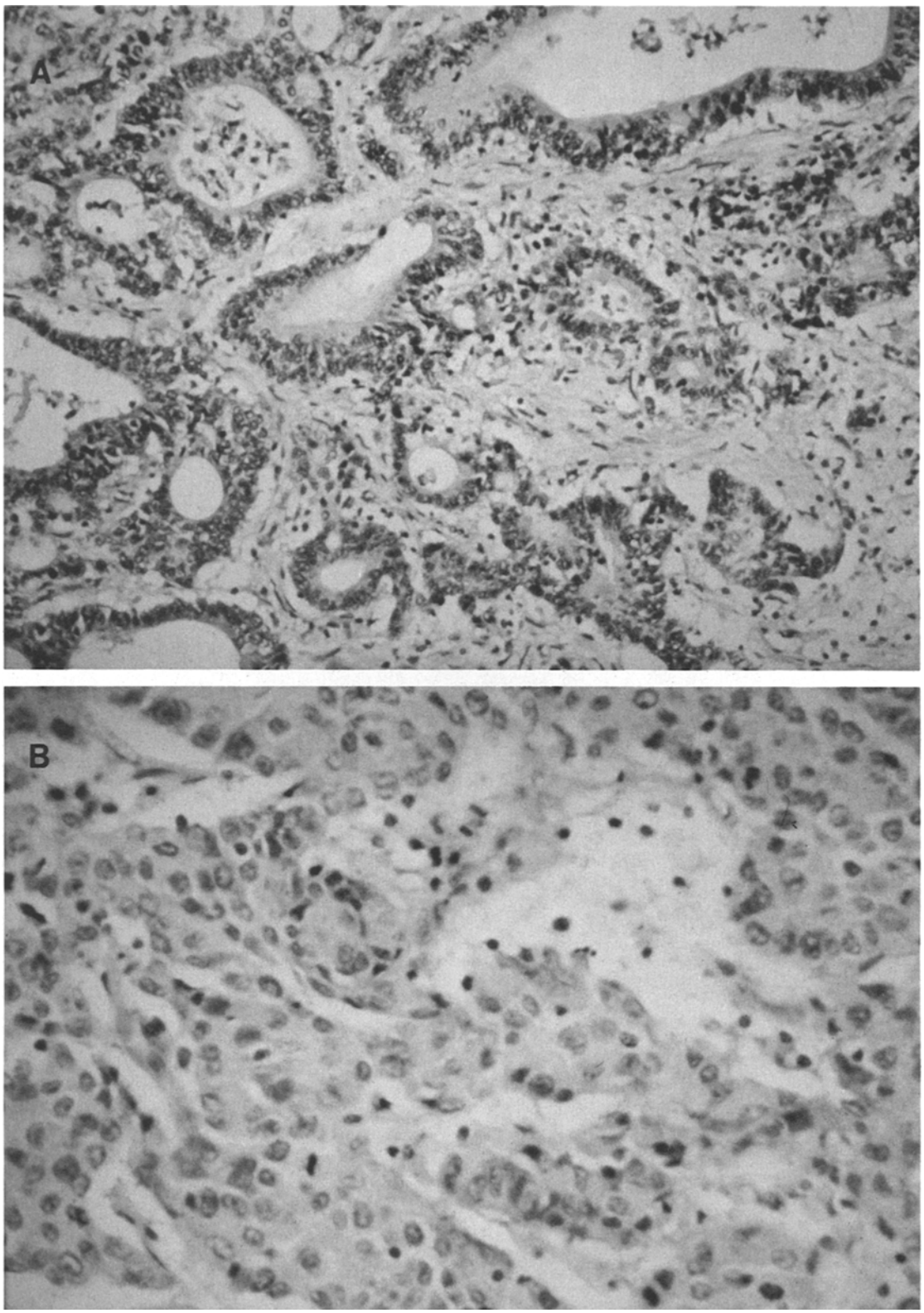

Fig 1. Light microscopic pictures of surgical specimen (patient 2). (A) Glandular areas of the tumor with moderate differentiation (H&E, ×200). (B) Organoid pattern of the tumor indicating the carcinoid nature of the tumor (H&E, ×400).

Serosal metastasis was shown to be carcinoid in nature in patient 3.

Electron microscopically (EM), cells from the adenocarcinoma areas demonstrated microvilli in their luminal surfaces (Figure 2A). Ultrastructurally numerous membrane-bound electron-dense neurosecretory granules with varying electrodensities were seen in the cells. The granules ranged from 100 to 350 nm in diameter (Figure 2B). No immunohistochemistry was performed to determined the hormonal content of these granules. Mucin was identified in EM studies within the adenocarcinoma cells (patients 4 and 5). No mucin was noted within the neuroendocrine cells themselves.

DISCUSSION

Composite tumors with histologic features of both carcinoid and adenocarcinoma are rare, and their biologic behavior is still unclear. Such tumors with combined characteristics have been found in various locations in the gastrointestinal tract including stomach, small intestine, appendix, colon, and gallbladder (5–28). A greater number of cases are in the appendiceal location, which is also the most common location of carcinoid tumors in the gastrointestinal tract (29) (Table 3). The aggressive clinical behavior of these tumors was recognized with serosal extension, perineural invasion, and metastasis to ovaries and liver (5–14). Edmonds et al, in their review of 86 cases of composite tumors arising from appendix, found that 51 were free of disease, 3 had persistent disease, and 11 died of disease following treatment by colectomy or appendectomy alone (14). Contrary to appendiceal composite tumors, we could not determine the prognosis of the composite tumors located in the colon. Ten such cases reported in the literature include information on the prognosis in only three of them. These patients were alive 8, 18, and 32 months after surgery (15–17). The literature on composite tumors of the colon concentrated more in the histopathologic evaluation of the removed tissue and omitted information on the clinical picture of these patients. Nine of 13 patients with colonic composite tumors were male (mean age: 58 years). Tumor commonly originated in the rectum and cecum and was evenly distributed in the proximal and distal bowel (Table 3). In all except one, tumor was out of the confinement of the bowel wall with metastasis to lymph nodes in 69%, liver in 23%, and peritoneum in 15% of the patients. These figures are higher than the risk of metastasis in colonic adenocarcinoma and significantly higher than the carcinoid tumors, signifying that the extension of the tumor is determined mainly by the magnitude of the carcinomatous part of the composite tumor (29–31).

Experience with gastric composite tumor is more limited than appendiceal or colonic composite tumors (15, 16, 21–26). There are a total of nine such cases, including ours in the literature. Although Rogers and Murphy reported 10 patients with adenocarcinoma of the stomach, which were found to have typical carcinoid differentiation on a subsequent histologic evaluation, in these cases, carcinoma and carcinoid parts were not individually recognizable (20). Therefore, they were correctly named as atypical carcinoids by the authors, and were not included in this analysis. The mean age of patients with gastric composite tumors were not different than patients with colonic composite tumors (55 years vs 58 years). Sex was recorded in six patients of which five were male and one was female (16, 22–26). In seven patients the diseases were extensive, with lymph node metastasis in five (5, 16, 23, 24), infiltration to omental fat in one (26), and to serosa in one patient (26). In two patients serosa and lymph nodes were free of metastasis (22, 25). Clinical course was mentioned in five of nine patients only. Three patients were alive, including our patient, 1, 14, and 36 months after the surgical removal of the tumor (23–25). The extent of lymph node metastasis as well as the depth of invasion seem to be more significant factors affecting survival than the histological pattern since the survival data in a large series of gastric adenocarcinoma reveals similar figures (32).

Only one patient with composite tumor in the small intestine was reported before (27). Tumor in this patient, as in our two patients, was localized in the proximal jejunum, in accordance with the most common location of adenocarcinomas in the small intestine and contrary to the common location of carcinoid tumors in the ileum (29). In two of these patients tumor extended to the serosa; in one the deep muscular wall was penetrated by the tumor. One of our patients is alive without metastasis 39 months after surgery, the other with local metastasis is alive 10 months after surgery but is receiving radiation and chemotherapy. No information is available on the outcome of the third patient (27).

The only patient described with composite tumor of the gallbladder is a 51-year-old female who died shortly after the operation and had partially ne-

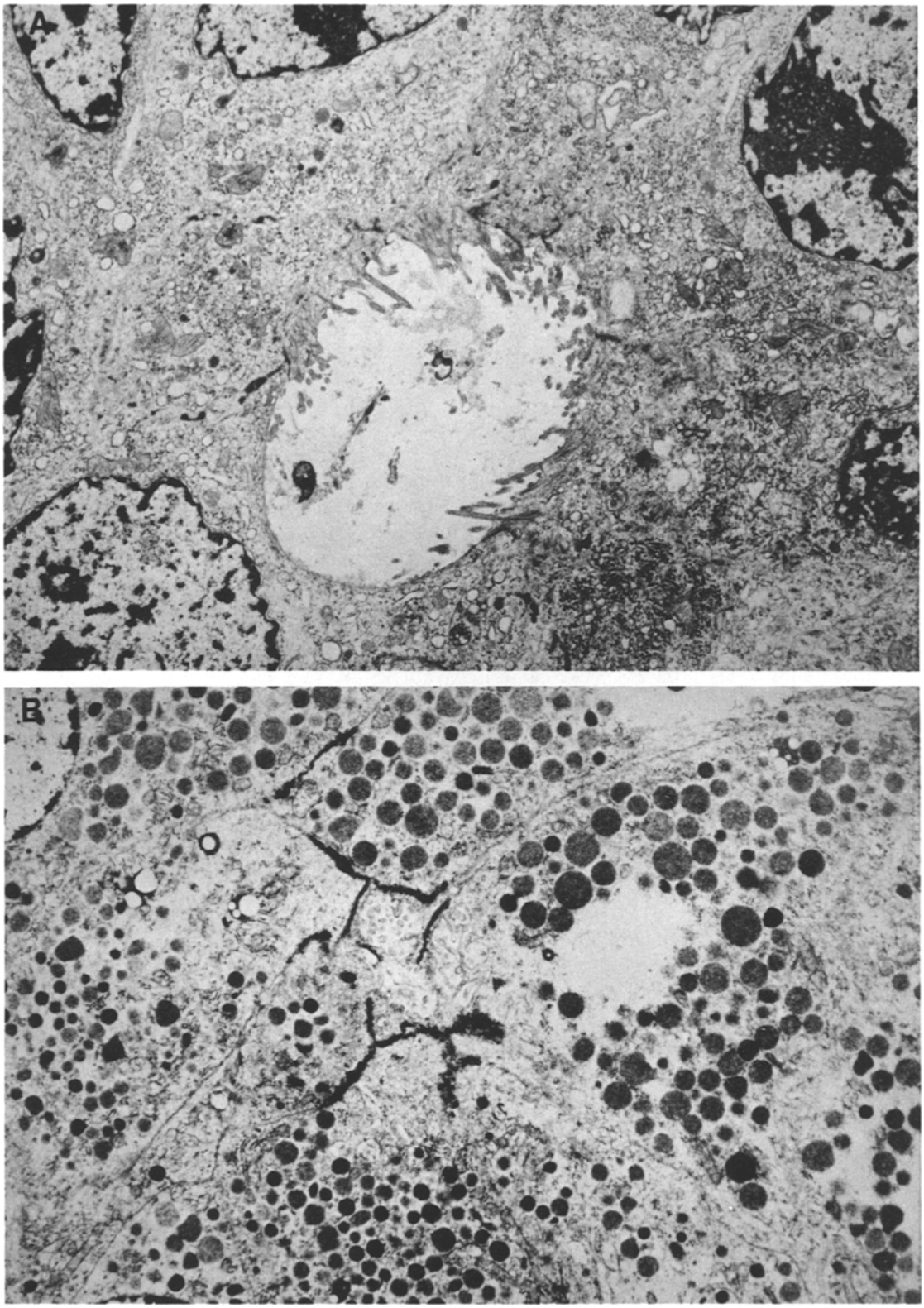

Fig 2. Electron micrographs from the same tumor tissue shown in Figure 1. (A) Lumen formation with microvilli indicating adenocarcinoma (×8700). (B) Typical membrane-bound electron-dense neurosecretory granules from the carcinoid portion of the tumor (×8700).

TABLE 3. DISTRIBUTION OF COMPOSITE TUMORS IN GASTROINTESTINAL TRACT IN 136 REPORTED CASES*

Location	*Patients* N (%)
Appendix	110 (80.9)
Colon	13 (9.6)
Cecum	3
Ascending colon	1
Transverse colon	2
Descending colon	2
Sigmoid	1
Rectum	4
Stomach	9 (6.6)
Small intestine	3 (2.2)
Gallbladder	1 (0.7)
Total	136 (100)

*Patients in this report are also included.

crotic tumor in the gallbladder with extension into the liver (28).

Through the review of the published patients and our patients, it may be anticipated that composite tumors can arise within organs containing both exocrine and endocrine components. Since secretory granules are present in the cells of the carcinoid part of these tumors, it may be expected that carcinoid syndrome could occur in these patients. Although various hormonal products were demonstrated histologically, none of these patients had clinical evidence of carcinoid syndrome (5, 13, 22). In three of our patients 5-hydroxyindole acetic acid in the urine determined postoperatively was found within the normal range. Rarity of the liver metastasis and organ of origin in some may explain the absence of carcinoid syndrome in these patients.

The histogenesis of composite adenocarcinoma–carcinoid tumors has not been fully characterized. Intimate arrangement with a sizable glandular and carcinoid component suggests a common histogenesis: either occurrence of coincidental malignant changes in two mature cell types (4) or a neoplastic change involving a common precursor cell (5). Such crypt basal cells from parent primitive endoderm with different levels of direction and differentiation would result in a variety of closely related tumors. Although carcinoid tumors arise from these cells, the origin of Kulchitsky cells, whether from neuroectoderm or gastrointestinal endoderm, is still unresolved (16).

From this review, we concluded that composite tumors most commonly arise in the appendix, localized in the jejunum in the small intestine, and behave more like an adenocarcinoma than carcinoid tumor regarding the extension of the tumor at the time of diagnosis. As for prognosis and survival, contrary to the former belief, composite tumors do not appear to have a better prognosis than ordinary adenocarcinoma (20, 21). Therefore, these patients have to be approached and treated more like patients with carcinoma than carcinoid.

SUMMARY

Tumors of the gut with composite features of both adenocarcinoma and carcinoid have been recognized mainly in the appendix. There also have been isolated reports of similar tumors arising from other parts of the gastrointestinal tract. It is generally concluded that these tumors have better prognosis than adenocarcinomas of the gastrointestinal tract. We reported six patients with composite tumors arising from the stomach in one, small intestine in two, cecum in two, and rectum in one patient. Clinical presentations in each was suggestive of malignancy with extension to either serosa and/or lymph nodes. Metastasis to liver was present in two patients. Histologically, the tumor showed glands with surface microvilli resembling adenocarcinoma and also organoid pattern with neurosecretory granules in cells resembling carcinoid. Two patients died three and nine months after surgery. The clinical presentation, findings at operation, and the postsurgical course of these six patients reveal that these tumors behave more like an adenocarcinoma than carcinoid and do not appear to have a better prognosis than ordinary adenocarcinoma.

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