Gastric Carcinoma Following Operation for Peptic Ulcer Disease

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Gastric carcinoma following operation for benign peptic ulcer disease has been considered rare but nine patients have been seen during the past five years. All were male patients, the average time interval from prior ulcer operation to development of cancer was 17 years, but was as short as ten years. The symptoms of cancer are vague and the diagnosis is often delayed. Fiberoptic endoscopy with biopsy of suspicious areas is the most accurate diagnostic approach. Resection of the tumor is indicated if feasible. The poor prognosis of this malignancy is documented. The evidence is reviewed that the creation of achlorhydria with bile reflux increases the risk of development of gastric carcinoma. All patients who undergo peptic ulcer operation require careful long-term follow-up. Vague gastrointestinal symptoms occurring ten years or more after peptic ulcer operation require full evaluation to exclude the presence of gastric cancer.

CARCINOMA OF THE STOMACH following operation for benign peptic ulcer disease is believed by many clinicians to be rare, and prior to the 1960's, few cases were documented. However, by 1972, Morgenstern et al.[13] were able to compile 1100 cases from the collected literature. These "stump carcinomas" have been noted following simple gastroenterostomy[5] or Billroth I resection[3] but are considered more likely after partial gastrectomy and gastrojejunal reconstruction (Billroth II).

The question frequently posed is whether there is more than a chance association between carcinoma of the gastric stump and a previous gastric resection. Swynnerton and Tanner[19] in 1953 found the risk of carcinoma of the gastric stump higher in patients after resection for gastric ulcer than in the normal population. Helsingen and Hillestad[8] described a higher incidence of carcinoma in patients who had undergone resection for benign gastric ulcer disease than in the normal population between 1919 and 1944, but no increase in cancer in patients undergoing resection for duodenal ulcer. Their review, however, preceded the clinical introduction of vagotomy.

Stalsberg and Taksdal[18] in 1971 in a large autopsy series reported a lower than expected incidence of gastric cancer in patients who had undergone operation for peptic ulcer disease less than 15 years prior to death, but a six fold greater than anticipated frequency of gastric cancer if operation had been performed more than 25 years prior to death. It is presumed that the early decreased risk is the result of smaller gastric mucosal surface area at risk initially after operation. Subsequently, in later series, the probability of developing cancer in a gastric remnant has been reported as high as 10%[9] but averages about 3%.[5] This is significantly higher than the spontaneous incidence of cancer of the intact stomach. The risk of developing stump cancer varies widely, but in each geographic area the risk of cancer in a gastric remnant appears to be substantially higher than the corresponding local risk of spontaneously developing gastric carcinoma in an unoperated stomach, and the probability of developing carcinoma in a remnant increases with time following operation.

This paper describes nine cases of carcinoma of the gastric remnant diagnosed at the Health Center Hospitals of Pittsburgh between the years 1972 and 1976, and reviews the evidence that gastric resection for peptic ulcer disease creates a milieu potentially favorable to the development of carcinoma.

Patient Identification

The records of 166 patients with carcinoma of the stomach at the Presbyterian-University Hospital of Pittsburgh and the Veterans' Administration Hospital, Oakland between 1972 and 1975 were examined. Six patients (3.6%) had a prior history of peptic ulcer disease treated by partial gastrectomy and gastrojejunostomy. Any patient who was previously operated upon for gastric cancer or benign tumor was excluded,

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Submitted for publication: July 7, 1977.

0003-4932-78-0300-0251-0075

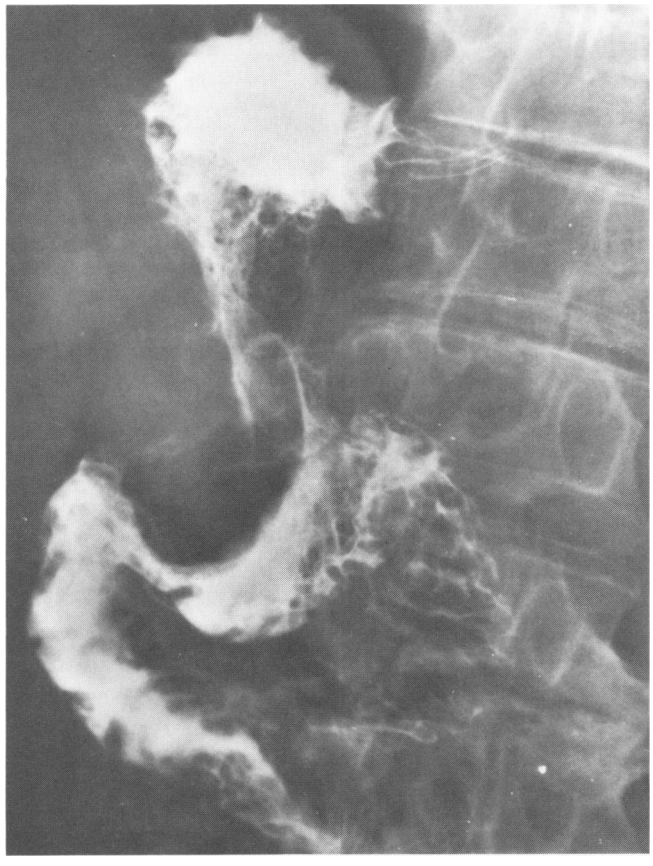

FIG. 1. Upper gastrointestinal barium contrast study of Patient 3 illustrating large compressing mass of the distal remnant.

as were patients who underwent peptic ulcer operation less than five years before the first evidence of carcinoma of the gastric remnant. All diagnoses were confirmed by histologic examination of biopsy material or surgical specimens. Three patients were identified prospectively during 1976 at the Health Center Hospitals of Pittsburgh.

Case Reports

Case 1. An 81-year-old man had a duodenal ulcer in 1960, treated by a two-thirds gastrectomy. The patient did well until 1966 when a recurrent ulcer was diagnosed and subsequently treated by a further gastrectomy. The patient again did well until 1971, when he noted low anterior chest pain similar to his earlier ulcer pain. The pain was aggravated by swallowing, progressed to severe dysphagia with evidence of gastroesophageal obstruction, and was accompanied by a 30-pound weight loss over one year. An endoscopic biopsy showed a mucinous adenocarcinoma of the gastric remnant. The patient received several courses of 5-Fluorouracil until he began to show evidence of drug toxicity. He expired 18 months following initial diagnosis.

Case 2. A 57-year-old man had a history of abdominal pain characteristic of duodenal ulcer disease beginning at age 21. At age 35 the patient underwent a Billroth II resection resulting in complete relief of symptoms for 20 years. For the last two years, the patient again experienced abdominal pain, but differing from his previous ulcer pain. It was characterized as a tightness or pressure in the midabdomen and epigastrium, made worse by eating solids, and relieved by drinking alcohol. He also complained of dysphagia, diarrhea, melena, and a 10-pound weight loss the preceding year. There was a 10 cm × 9 cm mass in the midabdomen above the umbilicus on physical examination.

Roentgenographic findings suggested a large mass surrounding the stomach. The patient underwent exploratory laparotomy which verified a large tumor beneath the omentum arising from the stomach. The biopsy was interpreted as a "signet ring" adenocarcinoma. The tumor was considered unresectable and the patient was started on a course of 5-Fluorouracil therapy plus radiotherapy. He expired several months after exploration.

Case 3. A 60-year-old man first exhibited ulcer symptoms 22 years prior to the diagnosis of gastric carcinoma. Twenty years prior to diagnosis of cancer the patient underwent a Billroth II resection with complete relief of symptoms except for very mild and occasional epigastric pain relieved by antacids. Three years prior to diagnosis, the patient had melena, and an upper gastrointestinal series showed prominent gastric folds and a questionable anastomotic ulcer. At exploratory laparotomy he had friable gastric mucosa but no ulcer. One year later the patient had a suspicious upper G.I. series (Fig. 1), but gastroscopy at that time showed only hypertrophic gastritis. Repeat gastroscopy ten months later showed bile-stained gastric contents with evidence of acute and chronic inflammation of the gastric remnant. Biopsy showed nonspecific inflammatory changes.

Subsequently, the patient developed greatly increased weakness, melena and weight loss. He had a normal abdominal examination without a mass. Gastroscopy showed an active ulcer 1½ cm in diameter on the gastric side of the anastomosis covered with necrotic exudate and fresh blood. Biopsy showed adenocarcinoma and the patient underwent a thoracoabdominal total gastrectomy, jejunojejunostomy and an esophagojejunostomy. Mesenteric infiltration was noted as well as perineural and vascular invasion. No tumor was found in any of the lymph nodes examined.

The patient did well after operation for one year, but developed jaundice and the presence of liver metastases was confirmed. The patient was begun on 5-Fluorouracil therapy, but expired several months later.

Case 4. A 55-year-old man with a long history of peptic ulcer disease underwent a Billroth II resection 13 years prior to the diagnosis of stump cancer. He did well until three months prior to diagnosis when he exhibited symptoms of anorexia, early satiety, dysphagia, and a 20-pound weight loss. Physical examination was entirely normal. He was anemic but had negative stool guaiac examinations. An upper G.I. series showed a filling defect of the stomach interpreted as a mass on the lesser curavature. Gastroscopy demonstrated an infiltrating, ulcerating lesion of the proximal gastric remnant. Biopsy was positive for adenocarcinoma. A metastatic evaluation was negative.

The patient underwent a total gastrectomy, splenectomy and esophagojejunostomy with a jejunojejunostomy and a feeding jejunostomy. The histology of the operative specimen showed, in addition to a mucinous adenocarcinoma, hyperplasia, and intestinalization of the gastric mucosa.

Postoperatively the patient developed an esophageal anastomotic leak with subsequent subphrenic and subhepatic abscesses. The patient died from sepsis one month postoperatively.

Case 5. A 66-year-old man with a 20-year history of duodenal ulcer disease was treated non-operatively until 1964 when he underwent a partial gastrectomy and a Billroth II anastomosis. He did well thereafter for 11 years until he presented with a 15-pound weight loss, decreased appetite and pain in his epigastrium, especially after meals and upon deep inspiration. Physical examination demonstrated a nontender epigastric mass, hepatomegaly and guaiac positive stools.

Upper G.I. series showed a functioning Billroth II gastrectomy and a probable mass in the stomach (Fig. 2). Gastroscopy demonstrated a 3 cm × 4 cm mass of the anterior gastric wall near the esophagogastric junction. The mass was soft and smooth but friable. Multiple biopsies were interpreted as chronic gastritis but malignancy was suspected. At laparotomy the tumor infiltrated the serosa and periserosal adipose tissue. The patient underwent subtotal gastrectomy, enteroenterostomy and gastrojejunostomy. The specimen on microscopic examination showed pleomorphic, hypochromatic, columnar cells in glandular arrangements, diagnostic of moderately well differentiated mucinous adenocarcinoma. Postoperatively the patient developed an anastomotic leak and expired from septic complications.

Case 6. A 66-year-old man first had duodenal ulcer disease diagnosed in 1942. The patient had operative closure of ulcer perforations in 1942 and 1944. In 1947 he submitted to gastric resection and Billroth II reconstruction. Despite chronic alcohol abuse, he did relatively well until 1973, when he presented with symptoms of "hurting all over," vomiting and a 25-pound weight loss. On physical examination he was icteric and had a large, tender mass in his right upper quadrant and epigastrium.

An upper G.I. series showed a questionable mass in the distal stomach (Fig. 3). A barium enema showed a constricting lesion of the transverse colon. Liver and spleen scans were suggestive of metastatic disease. Gastroscopy demonstrated a primary carcinoma of the stomach and biopsy confirmed undifferentiated adenocarcinoma. The patient had a progressive downhill course and expired one and one-half months later. Autopsy confirmed advanced adenocarcinoma of the stomach metastatic to the peritoneum, omentum, peripancreatic and periaortic nodes. There was partial obstruction of the transverse colon by encircling tumor, as well as severe bile duct obstruction. The jejunum was spared from the invading tumor.

FIG. 2. Upper gastrointestinal series of Patient 5 illustrating constricting mass at the gastrojejunal anastomosis.

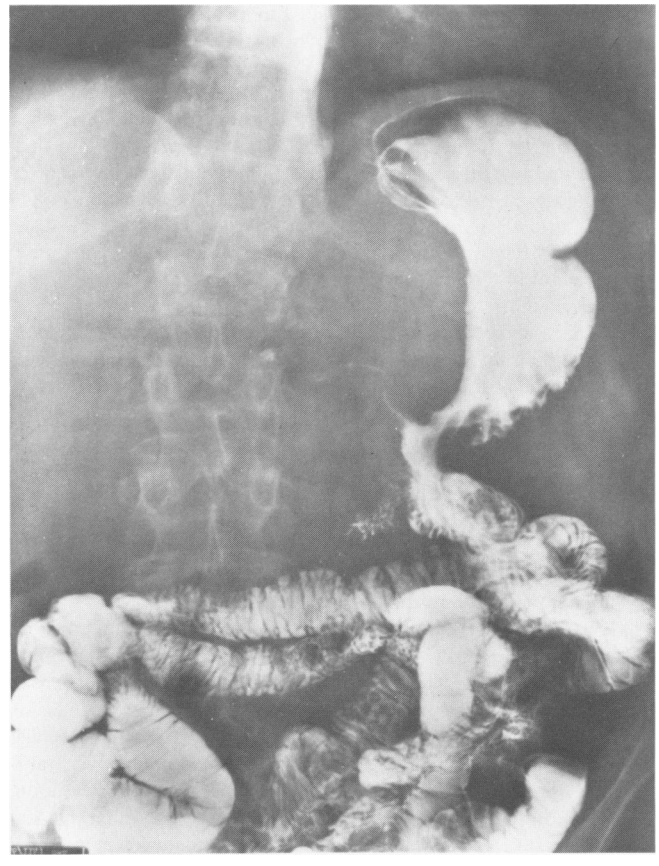

FIG. 3. Upper gastrointestinal series of Patient 6 illustrating mass of distal greater curvature.

Case 7. A 62-year-old man had a long history of chronic ethanol abuse and symptomatic ulcer disease. Twenty-one years prior to his diagnostic admission he underwent a Billroth II resection. The patient did well until the last three months prior to diagnosis, when he first noted a gradual onset of vague retroxyphoid and left epigastric pain when eating. The pain worsened as the meal progressed and was more intense after swallowing. He had occasional regurgitation of undigested food. He also experienced a 32-pound weight loss over the preceding three months. On physical examination he was cachectic and had hepatomegaly. Stool was guaiac negative and there were no masses or tenderness palpable in the abdomen.

An upper G.I. series demonstrated a lengthy narrowing of the distal esophagus suggestive of a semi-circular submucosal mass and a normally functioning Billroth II anastomosis. Abdominal sonagram, barium enema, IVP, brain, bone and liver/spleen scans were all within normal limits. An adult endoscope could not be passed beyond the distal esophagus, but a pediatric scope confirmed by biopsy the presence of poorly differentiated adenocarcinoma.

The patient underwent gastric resection, splenectomy, resection of the gastrojejunostomy and a Roux-en-Y esophagojejunostomy reconstruction. The tumor was metastatic to one esophageal node, two of three celiac nodes and ten local lymph nodes. The patient was well six months postoperatively, except for mild, vague abdominal pain.

Case 8. A 57-year-old man had symptoms of peptic ulcer disease most of his adult life. He underwent a Billroth II operation 12 years earlier and remained well for the next ten years. Approximately three months prior to diagnosis, the patient experienced the insidious onset of weakness and a 20-pound weight loss. He noted decreased appetite and a "hang up" of food in his distal esophagus. Physical examination was normal except for a slightly positive stool guaiac.

An upper G.I. series demonstrated a smooth induration of the esophagus just proximal to the gastroesophageal junction with slight dilatation of the distal esophagus and a large lobulated filling defect in the fundus of the stomach. Gastroscopy showed an obvious malignant tumor of the gastric remnant. Cytology was positive for malignant cells, and biopsy confirmed adenocarcinoma. The patient underwent gastrectomy, including resection of the gastrojejunostomy, splenectomy and esophagojejunostomy.

Pathologic examination showed a moderately well differentiated, infiltrating adenocarcinoma of the cardia of the stomach. The tumor invaded serosa in several areas, however none of the 29 lymph nodes examined contained tumor. In areas uninvolved by tumor, chronic gastritis, esophagitis and jejunitis were apparent. The tumor did not infiltrate the jejunum. The patient is now ten months postoperative and without evidence at present of metastatic disease, and has been maintained on 5-Fluorouracil.

Case 9. A 74-year-old man was admitted for intermittent episodes of flank pain during the preceding year without other genitourinary complaints. One month prior to admission he had experienced an episode of painless hematuria. Physical examination upon admission was normal. Laboratory data were normal except for mild azotemia. Benign prostatic hypertrophy was diagnosed and he underwent transurethral resection. Several days prior to the operation he began to complain of dysphagia. More detailed history revealed that this had existed for approximately one year, with a 40-pound weight loss, and that he had undergone a Billroth II resection for peptic ulcer disease ten years previously.

An upper G.I. series showed a stricture of the distal esophagus near the cardioesophageal junction. Endoscopy demonstrated a grossly deformed and necrotic gastroesophageal junction. The remainder of the stomach and duodenum appeared normal. Biopsy confirmed the diagnosis of poorly differentiated adenocarcinoma.

The patient underwent a thoracoabdominal esophagogastrectomy and esophagojejunostomy with resection of the old gastrojejunostomy. He developed a left hemothorax several hours postoperatively requiring re-exploration for control. The patient had a progressive downhill course with renal failure, hypotension, arrythmias and expired.

Discussion

The risk of spontaneous gastric carcinoma in the overall United States population is approximately 1.7%. Gastric carcinoma may occur in either sex and at any age, but is rare before the fourth decade. Males are affected twice as often as females. In the present series of stump cancer, all of the patients were male, no doubt reflecting the greater prevalence of ulcer disease in the male population.

In our review, 3.6% of patients with gastric carcinoma had undergone prior peptic ulcer operation, a frequency similar to that reported by other authors.[5] The diagnosis of cancer in this series was made an average of 17 years after the original gastric resection for benign ulcer disease. The length of this latency period is highly significant and is somewhat shorter than the latency period reported by others.[11]

All of the patients in this group had previously undergone a Billroth II reconstruction. Some authors have stated that since gastric stump carcinoma is seen less often after Billroth I than Billroth II reconstruction that the gastrojejunal reconstruction is more prone to develop carcinoma of the gastric remnant. However, stump cancer has been reported following Billroth I reconstruction[3] and the apparent difference may reflect the infrequent employment of Billroth I reconstruction. This is clearly a possible explanation in Pittsburgh where Billroth I reconstruction has rarely been employed.

During the past 25 years, operative intervention for the treatment of duodenal ulcers has been chosen with increasing frequency. Further, the wide adoption of vagotomy in conjunction with antrectomy or pyloroplasty has lead to the successful production of hypochlorhydria or achlorhydria in most patients treated operatively. These factors, as well as the improved life expectancy, have undoubtedly contributed to the increased incidence of gastric stump carcinoma. Not only have apparently favorable conditions for carcinogenesis been created by peptic ulcer operation, but there is an enlarging pool of patients for whom the latent period has or will have elapsed.

Characteristically, each of the patients presented here remained relatively free of symptoms for long periods, ranging from ten to 26 years after their original peptic ulcer operation. The symptoms of stump cancer are usually vague and often mimic symptoms of the original peptic ulcer or other postgastrectomy syndromes. Symptoms, therefore, tend to be ignored by both patient and physician and a definitive diagnosis is too often made late in the course of the malignancy.[7,15] Berkowitz[1] has divided the symptoms of stump cancer into three groups: a) those simulating postgastrectomy syndromes, b) those simulating recurrent ulceration and, c) those suggesting advanced malignancy. In our series, anemia, weight loss, dysphagia, epigastric pain or heaviness, regurgitation, upper gastrointestinal bleeding (melena or hematochezia), and obstruction were present in decreasing order of frequency. A combination of these nonspecific symptoms were present in virtually each case.

Routine radiologic examination should be performed. It is difficult, however, to interpret a postoperative upper gastrointestinal contrast examination.[2] Rapid gastric emptying, anatomic distortion, and the subtle changes present in early stump cancer make the early radiologic diagnosis of cancer difficult. Nonethe-

less, the diagnosis of carcinoma was suspected by upper gastrointestinal series in seven of the nine patients in this series, albeit often late in the course.

Fiberoptic gastroscopy is more reliable, and should be employed routinely where symptoms or radiologic examination suggest the possibility of stump cancer. Gastroscopy should be combined with biopsy or brush cytology of suspicious mucosal areas, or on a random basis. In this series the practice was to rely on biopsy; Gibbs reported 100% accuracy in these patients utilizing exfoliative cytology.[6] In all but one patient in our series biopsy performed at the time of gastroscopy provided a definitive diagnosis.

Of our nine patients, one presented with metastases and eight underwent exploration. Seven had a technically resectable mass. Resection required completion of total gastrectomy and there were four postoperative deaths in this group. Of the three survivors, one succumbed to recurrent disease and two are alive at six and ten months respectively.

In addition to adenocarcinoma, histologic examination of the resected gastric remnants also demonstrated acute, chronic and atrophic gastritis, cystification of gastric glands, adenomatous transformation of the gastric mucosa and intestinalization of the gastric mucosa. Not all of these changes were seen in every specimen but a variety of combinations were encountered, most often atrophic gastritis, chronic gastritis and cystification of the gastric mucosa. In several specimens tumor growth into the distal esophagus was evident. However, in no case was there infiltration of the jejunal side of the anastomosis, as has been infrequently described by others. Thus, the concept of a "barrier mechanism" which abruptly terminates the carcinoma at the anastomosis may have some validity and the carcinoma appears to propagate largely in a proximal direction.

The above microscopic changes in the gastric mucosa (gastritis, cystification, intestinalization) have been seen experimentally and appear to be precursor lesions to overt carcinoma.[4,11] It is presumed that they are related to the constant reflux of bile and pancreatic secretion over the gastric mucosa. Morson[14] in 1955 described several cases of carcinoma arising from areas of the gastric mucous membranes that had been replaced by intestinal metaplasia. These histologic changes are analogous also to those seen with spontaneous atrophic gastritis and pernicious anemia.[17]

Pernicious anemia is associated with an increased risk of cancer of the stomach and is believed primarily related to the atrophic gastritis which accompanies pernicious anemia. Gastric carcinoma has been confirmed by biopsy in up to 10% of patients with atrophic gastritis, after an average latent period of 15 years.[20] Imai et al.[10] have reported a higher incidence of prior gastritis in the Japanese population developing cancer. Recently Ruddell et al.[16] in a study of 69 patients with gastric carcinoma found an inverse relationship between nitrite concentration and hydrogen ion concentration in the stomach of patients with gastric cancer, with the latter concentration being very low. They have suggested that neutral gastric juice contains metabolically active bacteria capable of generating nitrite from nitrate and of catalyzing nitrosation. Thus, it appears that the environment provided by hypochlorhydria or achlorhydria along with bile and pancreatic reflux, and the presence of high ingested nitrite concentration can lead to formation of carcinogenic nitrosamines. This represents a possible explanation for the increased incidence of gastric carcinoma in patients who have undergone surgery for benign peptic ulcer disease. In support of this hypothesis, Kowalewski[12] showed experimentally that the malignant transformation of gastric mucosa by a potent oral carcinogen is enhanced by prior vagotomy and gastric mucosal injury (ulcer).

Thus, the evidence seems compelling that the production of achlorhydria, which is the goal of peptic ulcer surgery, compounded by bile reflux, produces a milieu favorable to the long-term development of gastric carcinoma. The possibility of gastric carcinoma is one more reason why patients who have undergone gastric resections should continue periodic follow-up for the remainder of their lives.

Conclusion

Nine cases of gastric stump carcinoma following operation for benign peptic ulcer are presented and discussed. Patients averaged a 17-year interval between gastric resection and onset of symptoms of carcinoma. Early symptoms in general were vague and at best only suggestive of malignancy, often mimicking other postgastrectomy syndromes. Epigastric pain, weight loss, and esophagogastric obstruction were prominent late symptoms. Although upper G.I. roentgenography is useful, fiberoptic endoscopy and biopsy are the definitive diagnostic measures. Evidence is reviewed that the goal of peptic ulcer surgery (achlorhydria) may contribute to a milieu favorable to the long-term development of gastric carcinoma. Patients who have undergone gastric resection should be periodically evaluated for the remainder of their lives.

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