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Upper Gastrointestinal Neoplasia in Familial Polyposis

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Upper gastrointestinal (UGI) endoscopy was performed in 41 asymptomatic American patients with familial polyposis to assess the prevalence of gastric and duodenal polyps and to characterize their pathological features. Eighteen patients (44%) had UGI endoscopic abnormalities. Six patients had both gastric and duodenal lesions. Eight patients had only gastric polyps, and four had duodenal polyps only. The presence of other extracolonic expressions of polyposis had a suggestive but statistically insignificant correlation with UGI polyps. Patients with familial polyposis and duodenal adenomatous polyps are at high risk for the development of periampullary cancer; screening and identification of these individuals is recommended.

KEY WORDS: UGI polyps; familial polyposis.

Familial polyposis is a hereditary premalignant disorder which leads almost invariably to large bowel cancer if left untreated (1). As awareness of colonic polyposis has increased and prophylactic removal of the large bowel has been performed more widely, other inherited, life-threatening expressions, particularly upper gastrointestinal cancer and desmoid tumors have received increasing attention (2, 3).

Benign neoplasia in the upper gastrointestinal tract of polyposis patients has long been recognized (4–6), but only recently, stimulated by Japanese investigators (7–9), have endoscopic surveys of the prevalence of gastric and duodenal polyps been reported (10–14). Taken together, these reports identify a frequency of gastric polyps ranging from 39% to 100% and of duodenal polyps ranging from 46% to 93%. Most gastric polyps have been found to be hyperplastic, whereas most duodenal polyps have been adenomatous. Adenomatous changes have been also identified frequently in biopsies of the ampulla of Vater. Other reports have cited the presence of polyps throughout the small intestine (15–17).

In 1935, Cabot first reported periampullary cancer in a polyposis patient (18). Subsequent investigators have added further evidence of this association; polyps and cancer have also been observed more distally in the duodenum, the jejunum, and the ileum (16, 19, 20), as well as in bile duct and gallbladder epithelium (21, 22). Although gastric cancer has been linked with polyposis, there has been only one instance of this association reported from the United States (23).

Upper gastrointestinal neoplasia has not generally been regarded as a component of Gardner's

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syndrome. In 1953, Gardner and Richards (24) first defined the syndrome of familial polyposis with extracolonic expressions of epidermoid cysts, osteomas, and fibromas; later (25) they added dental abnormalities and desmoid tumors. As polyposis patients have been more intensively studied, these and other extracolonic associations have been observed to occur frequently, either in the proband or in a relative, and the utility of this eponymic distinction among polyposis cases has been questioned (2, 3, 10, 12).

We examined a group of 41 asymptomatic polyposis patients to assess the prevalence of gastric and duodenal polyps and to address their features, significance, and management. In this study, the term "polyposis" is used to designate the disease of all patients in our population.

MATERIALS AND METHODS

Upper gastrointestinal endoscopy was performed in 41 asymptomatic polyposis patients of the total study group of 62 polyposis patients entered in a chemoprevention trial. All 62 patients were offered upper gastrointestinal endoscopy but only 41 accepted. All 62 study patients had had a total abdominal colectomy and ileorectal anastomosis. Of the 41 patients who underwent endoscopy, 26 had them performed at Memorial Sloan-Kettering Cancer Center (MSKCC), 23 by one endoscopist, and the remaining 15 procedures were performed by endoscopists geographically convenient to the patient's home. At MSKCC, the procedure was performed with Olympus GIFXQ and GIFQ endoscopes. Informed consent was obtained from each patient.

One physician evaluated each patient for the presence and type of extracolonic expressions by careful physical examination. These findings were correlated with the observations made at upper gastrointestinal endoscopy. Endoscopic biopsies of representative gastric and duodenal polyps were obtained and reviewed by one pathologist.

RESULTS

Endoscopic Surveillance. Upper gastrointestinal polyps were found in 18 of 41 asymptomatic polyposis patients (44%). Among the 18 affected patients, the gastric mucosa alone was involved in eight (20% of total), the duodenal mucosa alone in four (10%), and the mucosa of both organs was involved in six (15%). The detection rate of polyps was the same whether the endoscopy was performed at MSKCC (12 of 26, 46%) or elsewhere (6 of 15, 40%).

Ten of 20 men (50%) and eight of 21 women (38%) had polyps. The mean age of the 10 men with UGI polyps was 39.8 years, whereas that of the 10 men without polyps was 36.0 years. The mean age of the eight women with UGI polyps was 32.5 years, whereas that of the 13 women without polyps was 29.9 years. Neither patients' sex nor age were significant variables. The distribution by age and sex of the trial patients who declined endoscopy paralleled those who had endoscopic evaluation.

Other extracolonic expressions of polyposis were found in 11 of 18 patients with UGI polyps (61%) and in nine of 23 without UGI polyps (39%) (Table 1). These differences were suggestive but not statistically significant ($P = 0.14$, Fisher exact test). Hence, 20 of the 41 patients (49%) in this endoscopic study had other extracolonic expressions; among all 62 patients entered in the chemoprevention trial, extracolonic expressions were found in 34 (55%).

Moreover, the type of extracolonic expressions did not differ between those patients with and those without UGI polyps. Among the 11 with UGI polyps, extracolonic expressions included: sebaceous cysts alone in four, sebaceous cysts and lipomas or fibromas in four, sebaceous cysts and papillary thyroid cancer in two, and osteomas in one. Among the nine without UGI polyps, extracolonic expressions included: sebaceous cysts alone in three, sebaceous cysts and lipomas or fibromas in three, sebaceous cysts and osteomas in one, lipomas only in one, and an intraperitoneal desmoid tumor and fibromatosis in one.

Endoscopic Findings. Gastric polyps were concentrated in the fundus and body of the stomach. Usually these polyps appeared as sessile nodules or mucosal excrescences, although a rare polyp had a narrow stalk. Polyps were very small, usually 2–3 mm in diameter, with several as large as 5 mm. They were diffuse or in clusters and were always multiple, ranging in number from two to more than 100, with the higher numbers being most common. In only two instances were gastric polyps confined

TABLE 1. UGI POLYPS IN 41 PATIENTS WITH FAMILIAL POLYPOSIS*

		Extracolonic expressions		
		Present	*Absent*	*Total*
UGI polyps	Present	11	7	18
	Absent	9	14	23
	Total	20	21	41

*$P = 0.14$, Fisher exact test.

either to the lesser curvature or to the antrum. The gastric mucosa was diffusely abnormal only in one patient, who had an associated biopsy-proven atrophic gastritis.

Duodenal polyps tended to be fewer and larger than the gastric polyps. Duodenal polyps were also sessile and confined primarily to the second portion of the duodenum. The more distal duodenum was not uniformly evaluated. Larger polyps ranging from 5 mm to 10 mm in diameter were observed in three of the nine patients with duodenal polyps. In four patients, two of whom had no duodenal polyps, a promient or enlarged duodenal papilla was identified. In contrast with gastric polyps, the mucosa underlying the duodenal polyps was different from the surrounding mucosa, looking paler and more granular.

Pathology. Seventeen of the 18 patients with endoscopic abnormalities had biopsies of the stomach or duodenum, or both. All were reviewed by the same pathologist. Of the 14 patients with gastric polyps, 13 had a biopsy. In four of the patients with gastric polyps, a few slightly atypical glands characterized by pseudostratification and somewhat compressed and hyperchromatic nuclei were noted. Little or no cytoplasmic mucin was seen in most of these glands. One polyp from the gastric fundus demonstrated slight atypia and variation in the size and shape of a nest of glands (Figure 1). In another one of these same four patients, a second fundal polyp was a hyperplastic polyp (Figure 2). This polyp was characterized by irregularly dilated and microcystic glands containing abundant mucus. There was no loss of nuclear polarity and no nuclear hyperchromatism. The lamina propria of this polyp was increased. A fifth patient had a small hyperplastic polyp of the fundus in addition to intestinal metaplasia of the adjacent stomach mucosa. Biopsies of gastric polyps in the remaining eight patients showed no noteworthy histopathologic changes.

Of the 10 patients with duodenal lesions, nine had a biopsy. Eight of the nine biopsies showed characteristic adenomatous changes (Figures 3 and 4). The only biopsy in which adenomatous change could not be identified was small and technically poor.

DISCUSSION

In general, we observed a lower prevalence of gastric and duodenal polyps in polyposis patients than other Western investigators have reported. Western investigators have found gastric polyps of

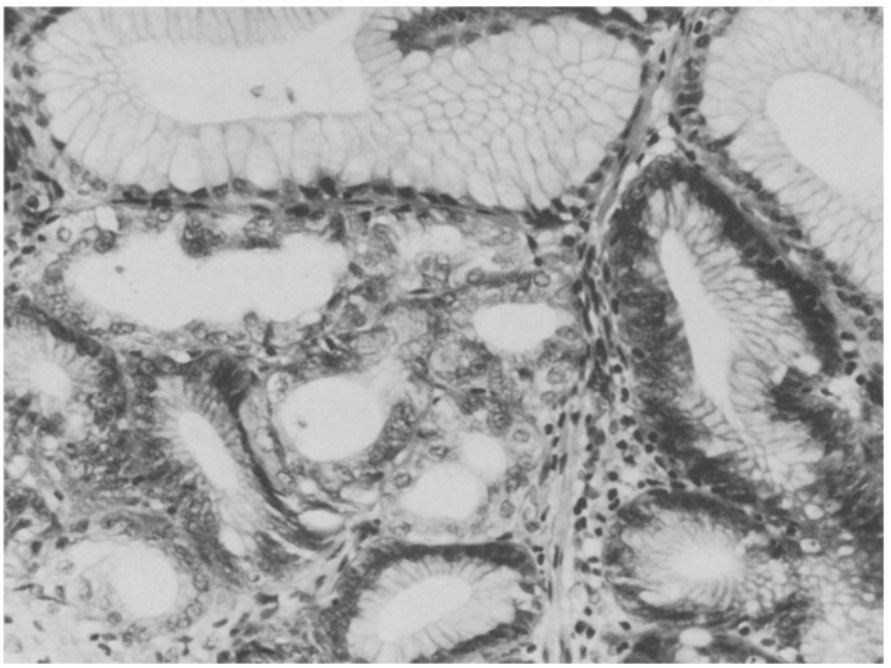

Fig 1. Gastric biopsy showing dysplastic gland at right and below. Note piled-up and hyperchromatic nuclei and somewhat diminished mucus. In center and at left is a focus of severe dysplasia with very irregular glands and enlarged nuclei with loss of polarity. 250×, H&E.

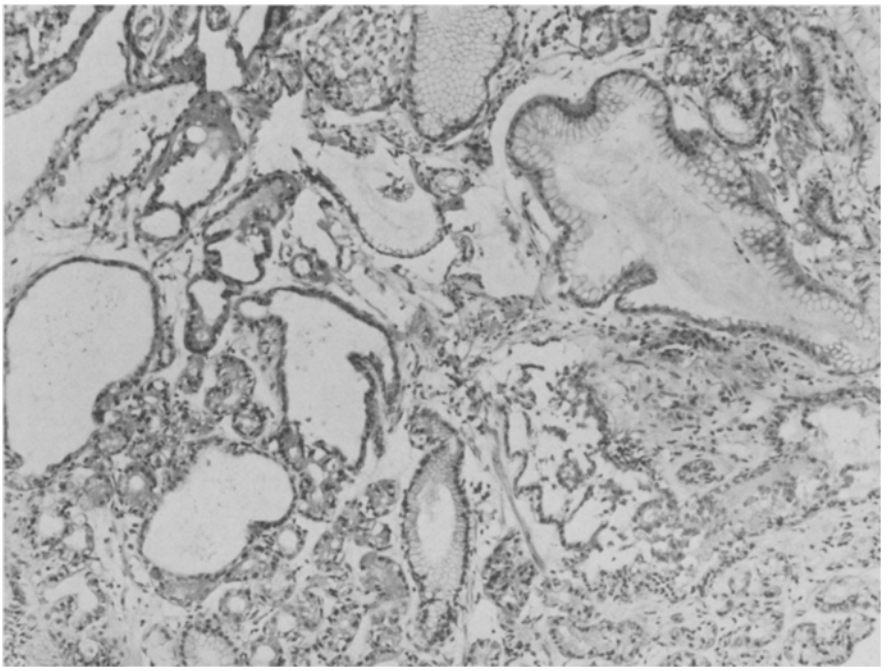

Fig 2. Hyperplastic polyps of fundus showing irregularly enlarged and cystic glands. Dysplasia is absent. 100×, H&E.

100% (14), 62% (11), 55% (13), and 39% (10) in contrast with 34% found in our study. In comparison, Japanese investigators have found gastric polyps in 68% (8, 9), 67% (7), 47% (26), and 39% (27) of

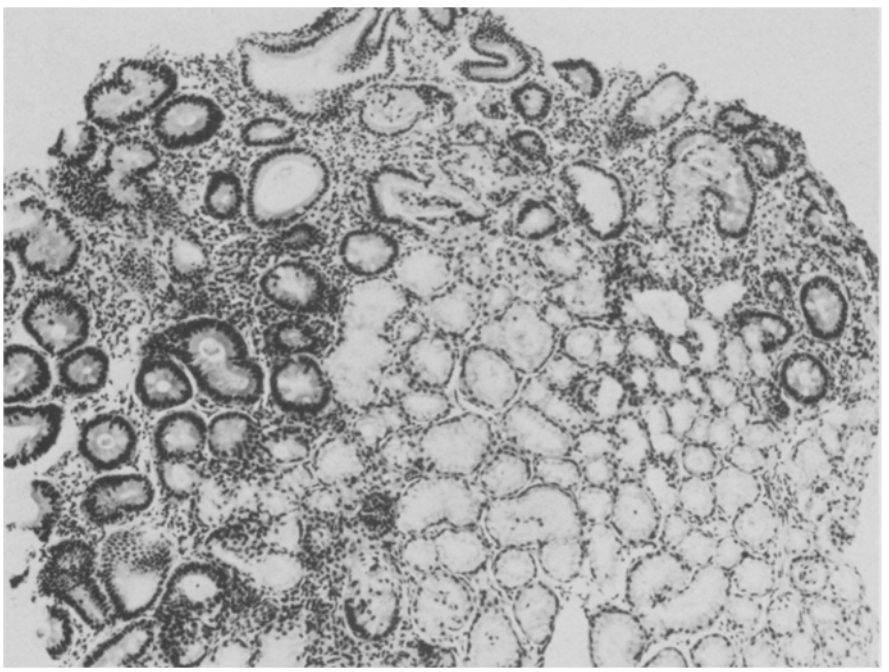

Fig 3. Duodenal biopsy revealing dark-staining adenomatous glands at left and at surface. 100×, H&E.

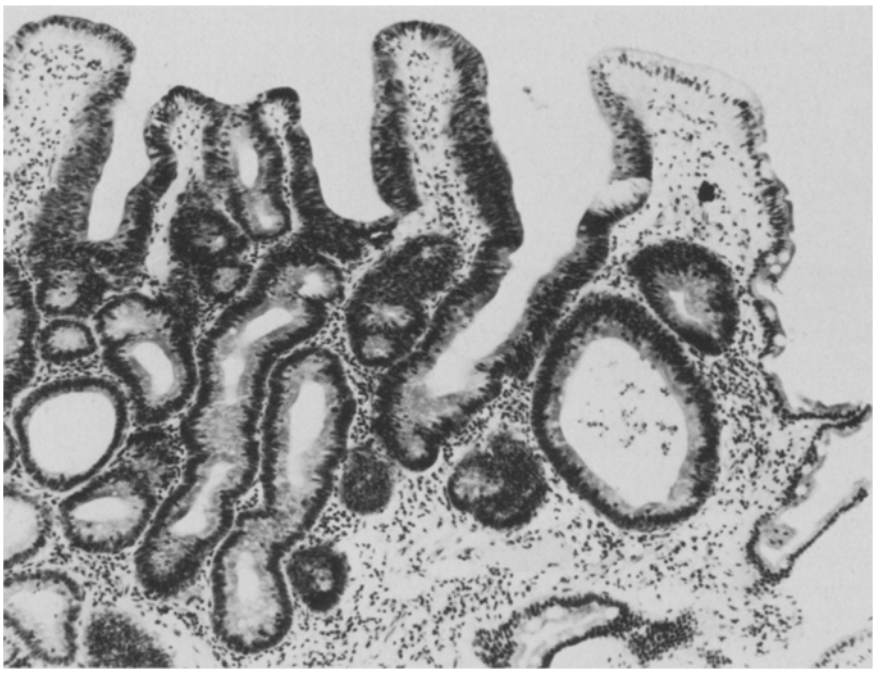

Fig 4. Adenomatous duodenal mucosa with only partial involvement of villous at right. 100×, H&E.

patients studied. Western investigators have found duodenal polyps in 89% (14), 73% (13), 61% (11), and 46% (10), in contrast with 24% in our study. Japanese investigators have found duodenal polyps in 93% (29) and 90% (8) (Table 2).

Reasons for our lower prevalence of gastric and duodenal polyps include lack of upper gastrointestinal symptoms in our patients, potentially different endoscopic techniques, and the use of radiological investigations in some series. Environmental or hereditary factors may play a role in the greater frequency of UGI polyps in the Japanese population. We feel that our results represent a reasonable estimate of the prevalence of UGI polyps, as determined by endoscopy in asymptomatic polyposis patients in the United States.

Our study confirms the regularity with which gastric fundal polyps are hyperplastic and duodenal polyps are adenomatous. There has been only one adenomatous polyp identified in the fundus of a polyposis patient (27): those few adenomatous polyps seen in the stomach occur only in the antrum.

We initially thought that the presence of other extracolonic expressions of polyposis might be a

TABLE 2. PREVALENCE AND LOCATION OF UGI POLYPS IN POLYPOSIS

Author (Ref)	*Patients studied*	*Gastric polyps*		*Duodenal polyps*	
		No.	*(%)*	*No.*	*(%)*
Jarvinen et al (11)	34	21	(62)	20	(61)
Bulow et al (10)	26	7	(39)	12	(46)
Burt et al (13)	11	6	(55)	8	(73)
Ranzi et al (14)	9	9	(100)	8	(89)
Utsonomiya et al (7)	15	10	(67)	—	
Watanabe et al (9)	22	15	(68)	—	
Nishiura et al (26)	34	16	(47)	—	
Iida et al (27)	31	12	(39)	—	
Ushio et al (8)	24	15/22	(68)	9/10	(90)
Yao et al (29)	14		—	13	(93)
Present study	41	14	(34)	10	(24)

clue to the need for endoscopy, but their presence in our study population made no difference in the observed frequency of UGI polyps. In a recent survey (12), more UGI polyps were found in patients who did not have other extracolonic expressions (50%) than in those who did (36%).

It is tempting to relate presence of adenomatous duodenal polyps in polyposis patients to the relatively higher frequency of periampullary cancer than gastric cancers in this population. Review of the polyposis patients at our institution revealed six cases of periampullary cancer and no instance of gastric cancer. There have been 32 patients with periampullary cancer reported (3, 30–32) and only 13 patients with gastric cancer, of which eight have been from Japan, a high-risk area for gastric cancer.

Does an adenoma–carcinoma sequence occur in the upper gastrointestinal tract of polyposis patients, as is generally believed to occur in the large bowel? The present evidence for this is circumstantial. (1) The distribution of adenomas parallels the sites for risk of cancer, being found regularly in the duodenum and rarely in the stomach. (2) The patient's age at detection of adenoma (not to be confused with the age of onset) precedes the age of detection of periampullary cancer by about 10 years and parallels patients with large bowel cancer. (3) Other duodenal adenomas are linked with periampullary cancer in the polyposis patient. (4) *In situ* and early invasive cancers are found within tubular, villous, and mixed adenomas in the duodenum of polyposis patients. (5) An 81.2% incidence of residual adenoma in ampullary carcinoma (33) suggests the relevance of duodenal adenomas as precursors of invasive cancer. Although these data do not prove causation, prudence suggests that duodenal adenomas should be approached with some vigilance.

When should UGI endoscopy be initiated in the asymptomatic polyposis patient? How often should it be performed? Should upper gastrointestinal radiography be added? What should be done when adenomas are found? What is accomplished by the endoscopic procedure?

None of these questions can be answered with confidence: all require further data for resolution. Within the limitations of what is now known, we suggest the following treatment policies for the polyposis patient without UGI symptoms. Any polyposis patient over the age of 20 who is awaiting large bowel surgery should have an UGI endoscopy. Otherwise, screening by endoscopy should start at age 30, although it should be noted that three periampullary cancers have been detected in younger patients. Gastric fundal polyps alone are innocuous: in these patients, UGI endoscopy should be repeated at five-year intervals, and radiography is unnecessary.

Duodenal polyps require closer scrutiny. When these are present, double-contrast radiography of the distal duodenum and jejunum should be performed. An abnormal papilla should be biopsied. Small (<5 mm) duodenal polyps may be monitored by periodic endoscopy. Larger duodenal polyps should be removed, preferably by endoscopic techniques or, if this is not possible, by surgical intervention.

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