Proton Pump Inhibitor–Associated Gastric Polyps

A Retrospective Analysis of Their Frequency, and Endoscopic, Histologic, and Ultrastructural Characteristics

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Abstract

Since 1992 there have been reports of proton pump inhibitors being associated with fundic gland–type gastric polyps. Endoscopic and histologic characteristics and natural history of these polyps have not been clearly defined. We performed a retrospective study of patients on long-term treatment with proton pump inhibitors who developed gastric polyps. Gastric polyps developed in 17 (10 males and 7 females, 7.3%) of the 231 patients who underwent 2 or more upper endoscopies for complicated gastroesophageal reflux disease and who were receiving long-term treatment with proton pump inhibitors. The mean interval of proton pump inhibitor use after which an endoscopy revealed gastric polyps was 32.5 months. In 1 patient, discontinuation of treatment resulted in disappearance of the polyps within 3 months. The polyps recurred 4 months after the treatment was restarted. Endoscopy established that typical polyps were generally small (<1 cm), sessile, multiple, and whitish pink with a mottled, partially translucent surface. The polyps were most often present in the proximal/midgastric body. Of the 15 polyps removed endoscopically, 9 were of the fundic gland type, 4 were of the hyperplastic type, and 2 were of the inflammatory type. Eight of 9 polyps with typical endoscopic appearance were of the fundic gland type. None of the polyps contained dysplasia or carcinoma. Long-term use of proton pump inhibitors may be associated with the presence of small gastric fundic gland polyps and hyperplastic polyps. A prospective study is required to establish their incidence, natural history, and clinical significance.

Proton pump inhibitors (PPIs) are a benzimidazole-substituted class of antisecretory agents. They have been available for general use in the United States since 1989. These small molecules decrease parietal cell acid secretion by inhibiting hydrogen/potassium-exchanging adenosine triphosphatase. This enzyme catalyzes the final step in the secretion of acid.[1–3] Major concerns regarding the long-term use of proton pump inhibitors and their possible role in causing gastric carcinoid tumors in humans appear to have been resolved.[4] The Food and Drug Administration recommendation that PPI therapy be limited to 2 consecutive months has been withdrawn. As more patients use these agents on a long-term basis, significant experience is being gained regarding other effects. One associated endoscopic finding, first reported in 1992, is the occurrence of gastric fundic gland polyps in patients on long-term treatment with PPIs.[5,6] Fundic gland polyps were first described by Watanabe and colleagues in 6 of 22 patients with familial polyposis coli.[7] Later, these polyps were also described in persons without polyposis coli syndrome.[8–10] They sporadically occur in the oxyntic mucosa of the stomach and are composed of normal-appearing fundic glands with an increased number of chief and parietal cells. Many of the glands are cystically dilated.[8–11] Despite several reports of fundic gland polyps developing in patients being treated with a PPI, detailed studies of the endoscopic, microscopic, and ultrastructural characteristics of these lesions have been lacking.

We performed a retrospective review of patients receiving maintenance PPI therapy to evaluate the morphology, histologic features, and ultrastructure of any polypoid lesions seen during the treatment period.

Materials and Methods

A database review was carried out to determine the number of patients who underwent evaluation by esophagogastro-

duodenoscopy (EGD) at the Center for Swallowing Disorders at the University of South Florida, during the period from March 1987 to February 1996 for various indications. We then determined the number of patients who were receiving long-term treatment with PPIs. Two groups of patients were identified. Group 1 included patients who underwent a single EGD and were not receiving long-term PPI treatment. Group 2 included patients who had undergone more than 1 EGD and had been started on long-term treatment with a PPI after their first EGD. The number of patients with gastric polyps in each group was determined. As is typical, patients in the group receiving long-term PPI therapy for complicated gastroesophageal reflux disease were evaluated more closely and underwent 2 or more EGDs. One of the authors (H.W.B.) was present for all endoscopies.

A detailed chart review of the patients reported to have gastric polyps was carried out, and the following data were recorded: patient demographics, indications for long-term use of PPIs, date of initiation of PPIs, name and dosage of the agent, date of EGD when polyps were absent (EGD_1), and the date of EGD when polyps were first reported (EGD_2). Also recorded were the location, number, size range of polyps in each patient, endoscopic appearance, color, and surface characteristics of the polyps. Furthermore, any changes in the type and dosage of PPI used, change in size, number, and surface appearance of these polyps on each EGD were also obtained from the endoscopy reports. Endoscopic photographs or videotapes of the EGD exams of these patients were reviewed. The available data were used to determine the interval of diagnosis of these polyps after initiation of PPIs, mean duration of PPI use, and correlation of change in the number of the polyps with a change/discontinuation of PPIs.

After they had been removed endoscopically, the polyps were fixed in formalin for not more than 12 hours, stained with H&E, and processed for routine histologic examination. Portions of 4 polyps, 2 with typical endoscopic appearance and 2 with a flat, atypical appearance, were fixed in 2.5% glutaraldehyde overnight at 40°C for electron microscopy. Briefly, these samples were washed in 0.1 M phosphate buffer and fixed in 1% osmium tetroxide for 1 hour at 4°C. The tissues were then dehydrated and embedded in LX112 epoxy resin (Ladd Corp, Burlington, Vt). Sections with a thickness of 85 nm were stained for 10 minutes in 8% aqueous uranyl acetate and 5 minutes in Reynold's lead citrate. Sections were examined with a Philips CM10 transmission electron microscope (Mahwah, NJ). For the scanning electron microscopy, samples from the same patients were dehydrated and then placed in 100% hexamethyldisilazane for 5 to 10 minutes. After drying, the tissue was mounted on a scanning electron microscope stub with silver paint, sputter-coated, and then examined.

Results

A total of 2,303 patients underwent EGD during the period for which the database was reviewed. Of those patients, 2,072 underwent EGD for established indications such as dysphagia, gastroesophageal reflux disease, and columnar lined esophagus but did not receive long-term treatment with PPIs (group 1). Fourteen (0.6%) of the patients (7 males and 7 females) in this group were reported to have gastric polyps. A review of these patients' records revealed that they all had gastric polyps visible at the time of their first endoscopy. The polyps were of the fundic type in 6 patients and of the hyperplastic type in 5 patients. One patient had both fundic and hyperplastic polyps, and 2 patients had inflammatory polyps. None of these patients underwent more than 1 endoscopy.

On the other hand, of 231 patients who were being treated with PPIs on a long-term basis and who underwent upper gastrointestinal endoscopy (group 2), 17 (7.3%, 10 males and 7 females) were found to have gastric polyps at the time of their second EGD. No patients in group 2 had gastric polyps at the time of their first EGD. Compared with the patients in group 1, the patients in group 2 were subjected to much closer follow-up because of the severity of their disease and because of their repeated need for dilation, esophageal biopsy, or both. The group 2 patients began treatment with a PPI at the time of their first EGD. The 17 patients in group 2 who were found to have gastric polyps had been receiving PPIs for a mean of 37.4 months (range, 3–98 months; median, 35 months) at the time of the review.

In 12 patients the polyps were seen in more than 1 gastric region. Polyps were seen in the proximal gastric body in 13 patients, midbody in 11 patients, gastric fundus in 7 patients, and distal body in 3 patients. Eight patients had between 1 and 10 polyps (3 had a solitary polyp), 1 patient had between 11 and 20 polyps, and 8 patients had more than 30 polyps. The mean interval between when patients began receiving a PPI and EGD_1 was 17.2 months (range, 0–96). The mean duration between initiation of PPI and EGD_2 was 32.5 months (range, 2–98 months). Omeprazole was the most commonly used agent, and it was most commonly administered in a dose of 20 mg daily (to 13 patients). Two patients received omeprazole in a dose of 20 mg twice daily after initially receiving 20 mg daily. Two other patients received 30 mg of lansoprazole daily. One of these 2 patients had received omeprazole in a dose of 20 mg daily before being started on lansoprazole. There was no correlation between the dose of PPI or duration of its use and number of gastric polyps.

Four patients underwent a third EGD between 2 and 21 months after their second EGD (mean, 8.5 months; median, 8 months). Three of these patients had no change in their medication regimen during this period. The fourth patient's PPI was discontinued. The latter patient's polyps disappeared completely 3 months after discontinuation of PPI therapy; however, his polyps reappeared 4 months after resumption of the PPI. Of the 3 patients whose PPI regimen was not changed, 1 showed an increase in the number of polyps. The number and size of polyps remained the same in the other 2 patients.

Endoscopic Characteristics

At endoscopy, the PPI-associated polyps were generally small (2–5 mm), sessile, multiple, and whitish pink with a mottled or smooth, partially translucent surface **Image 1, A**. They were located in the fundus, proximal, and midbody of the stomach. The smallest form of these polyps appeared as mucosal "mammilations." The translucent spots on the polyp surface produced minute elevations and depressions. These polyps were very soft and usually detached in toto when subjected to a biopsy. Because of their small size, the polyps were often hidden between rugae and became visible when the stomach was fully distended. This endoscopic appearance was considered typical of PPI-associated polyps by the endoscopists. Histologic examination established most of these polyps to be of the fundic gland type. Some other polyps were found to have an irregular shape and a flat surface with undistinguishable surface details **Image 2, A**. These polyps were usually seen in clusters and were determined by histologic examination to be of the hyperplastic type.

Histologic Characteristics

Of the 15 polyps (from 15 of the patients in group 2) on which biopsies were performed, 9 were of fundic gland type, 4 were of the hyperplastic type, and 2 were of the inflammatory type. Microscopically, fundic gland polyps were composed of cystic, dilated fundic glands lined with both parietal and chief cells **Image 1, B**. The hyperplastic polyps were recognized by the dilated, elongated, and branched foveolae lined with mucous cells only **Image 2, B**. No pseudostratification, mitotic activity, or dysplasia was seen in these polyps. In 2 patients, the polyps were of the inflammatory type and were characterized by a polymorphic inflammatory stroma, rich in eosinophils, surrounding cystically dilated glands. In 89% of the patients with typical polyps, cystic dilatation of the fundic glands was a prominent histologic finding. In 2 patients, both hyperplastic and fundic type gastric polyps were detected on EGD.

Ultrastructural Characteristics

Examination of the fundic gland polyps by scanning electron microscopy revealed a bumpy surface with donutlike gastric crypts **Image 1, C**. At higher magnification, the luminal surface of these polyps was shown to be a mixture of small round cells covered with short microvilli and larger oval cells demonstrating pronounced central domes **Image 1, D**. Transmission electron microscopy showed that the rounded cells were actually elongated cells with a basally located nucleus and zymogenlike material filling the apical portion of their cytoplasm. Interspersed among these cells were mucus-secreting cells **Image 1, E**. In contrast, hyperplastic polyps showed a cerebriform surface with large convoluted openings **Image 2, C**. At higher power, the apical surface of monotonous ovaloid cells was ringed with short microvilli **Image 2, D**. By transmission electron microscopy, these cells were exclusively elongated mucus-secreting epithelial cells **Image 2, E**.

Discussion

The incidence of all types of gastric polyps found by endoscopy is about 3% to 5%.[12–14] Gastric polyps occur more frequently in certain conditions, with incidences of 22% in cases of pernicious anemia,[15,16] 6% in cases of chronic atrophic gastritis,[17] and 4% to 20% after partial gastrectomy.[18,19] They also occur more frequently in hereditary gastrointestinal polyposis syndromes. The majority of these polyps are benign.[20] Gastric polyps may be subdivided into hyperplastic, adenomatous, hamartomatous, inflammatory, and heterotopic types. Of these, the adenomas are premalignant lesions and the other types are traditionally considered benign, although hyperplastic polyps may have a low incidence (1%–2%) of malignant change.[21,22]

The association between gastric polyps and prolonged use of omeprazole was first suggested in 1992 by Graham, who reported fundic gland polyps in 4 of 11 patients who had received omeprazole for 12 months or longer.[5,6] The author observed a statistically significant difference upon comparing his finding to the observation that, of 295 patients not receiving omeprazole, only 3 developed fundic gland polyps during the same period ($P < .001$). In our series of 231 patients who were being treated with PPIs on a long-term basis and who underwent upper gastrointestinal endoscopy, 17 were found to have gastric polyps while receiving PPIs. When that figure was compared to the number of polyps (14) seen in patients not being treated with a PPI (n = 2,072), a statistically significant ($P < .001$) difference was found. Interestingly, in 1 of these patients, the polyps disappeared after cessation of PPI therapy and reappeared when the therapy was reinstituted. Estimation of the frequency of this finding requires further study.

There has been disagreement among different authors regarding the histologic characteristics of PPI-associated polyps. In his report of 5 cases, Stolte described multiple,

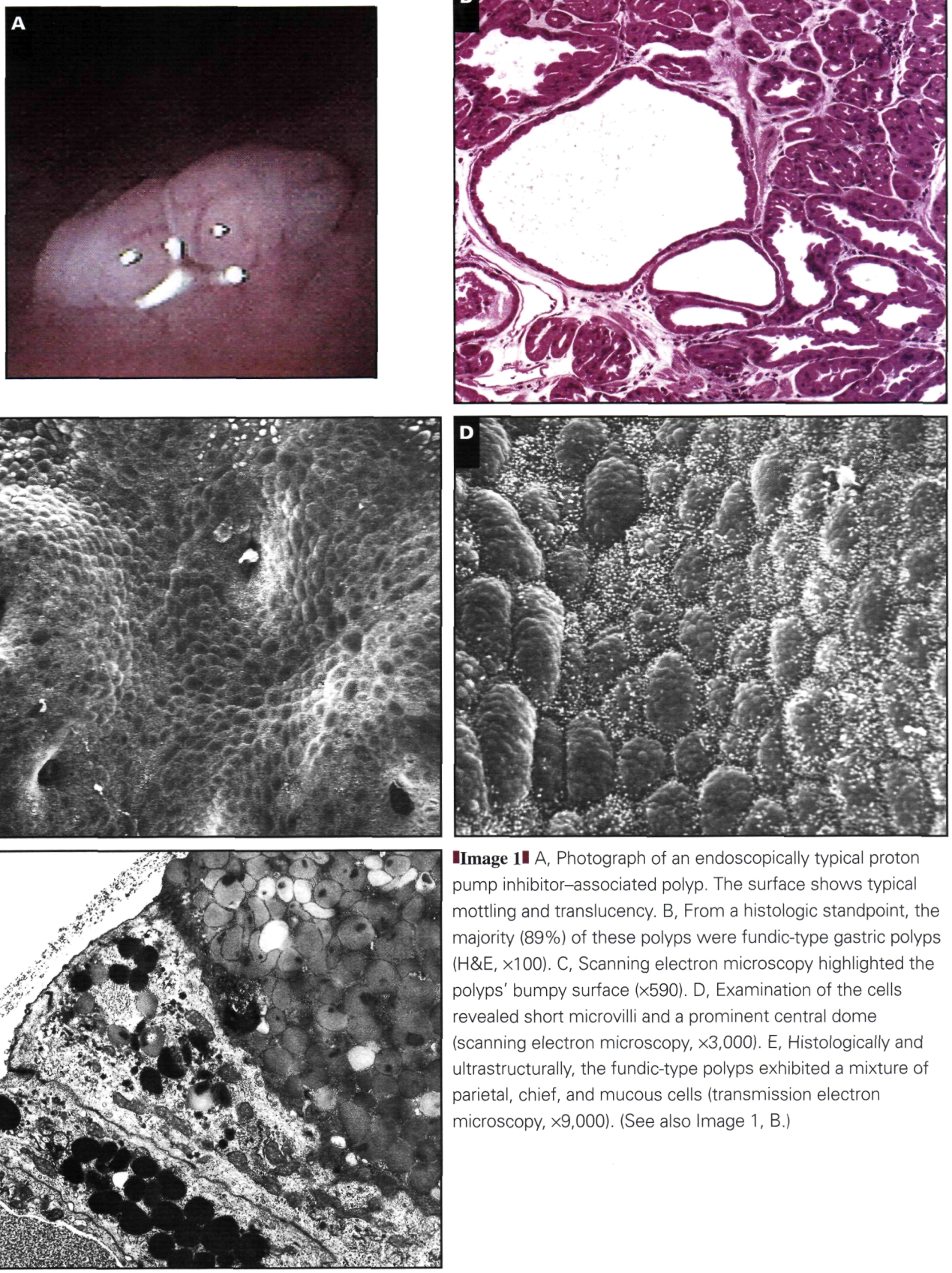

Image 1 A, Photograph of an endoscopically typical proton pump inhibitor–associated polyp. The surface shows typical mottling and translucency. B, From a histologic standpoint, the majority (89%) of these polyps were fundic-type gastric polyps (H&E, ×100). C, Scanning electron microscopy highlighted the polyps' bumpy surface (×590). D, Examination of the cells revealed short microvilli and a prominent central dome (scanning electron microscopy, ×3,000). E, Histologically and ultrastructurally, the fundic-type polyps exhibited a mixture of parietal, chief, and mucous cells (transmission electron microscopy, ×9,000). (See also Image 1, B.)

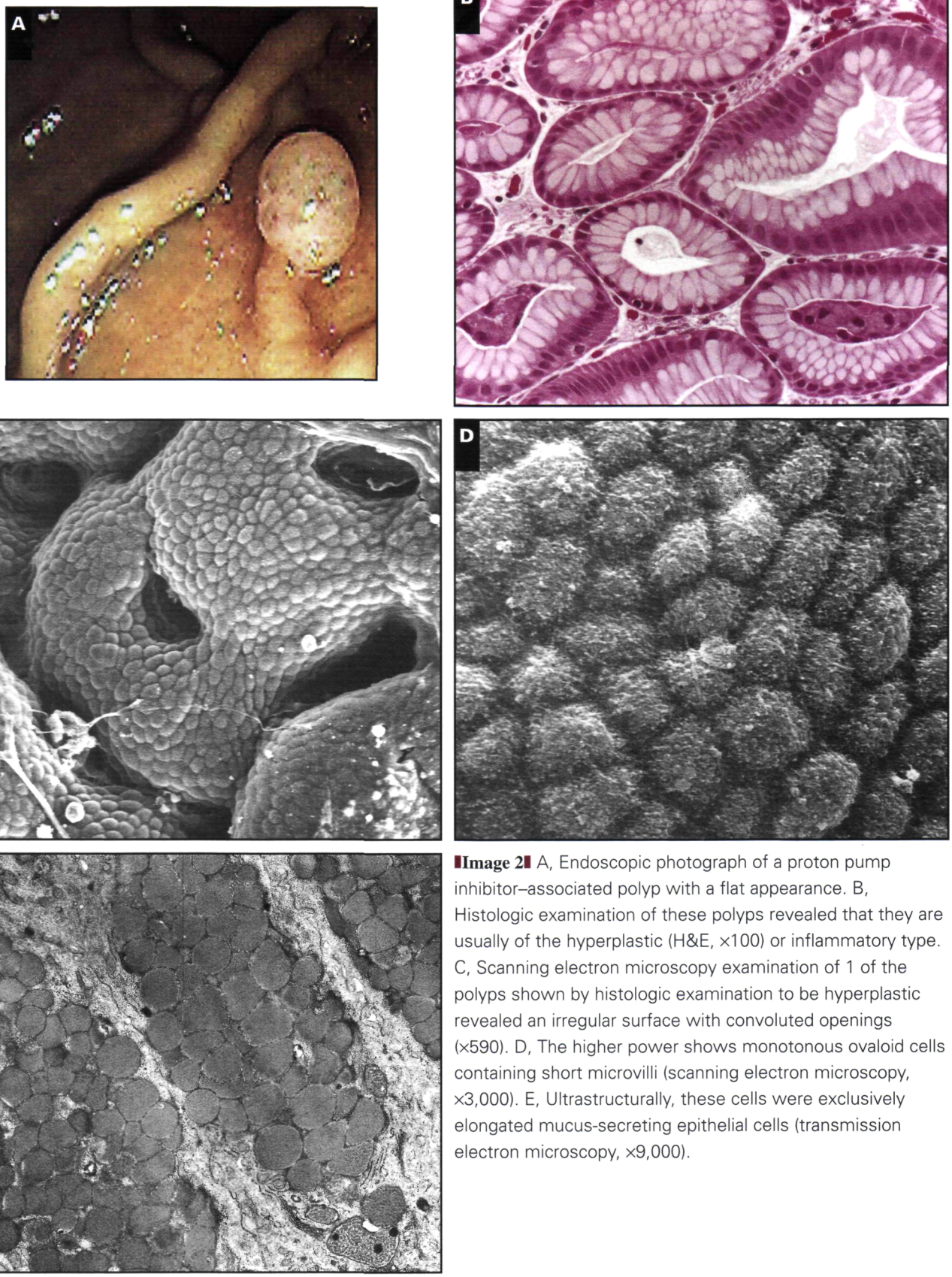

Image 2 A, Endoscopic photograph of a proton pump inhibitor–associated polyp with a flat appearance. B, Histologic examination of these polyps revealed that they are usually of the hyperplastic (H&E, ×100) or inflammatory type. C, Scanning electron microscopy examination of 1 of the polyps shown by histologic examination to be hyperplastic revealed an irregular surface with convoluted openings (×590). D, The higher power shows monotonous ovaloid cells containing short microvilli (scanning electron microscopy, ×3,000). E, Ultrastructurally, these cells were exclusively elongated mucus-secreting epithelial cells (transmission electron microscopy, ×9,000).

small polypoid elevations in the oxyntic mucosa.[23] Histologically, the author described gastric glandular cysts, which he called "Elster cysts." He hypothesized that these polyps resulted from the change in gastric secretion during omeprazole therapy.[23] The cystic nature of these polyps was also described by Dent and colleagues, who remarked on the benign nature of the lesions and the questionable relevance to the postulated linkage with omeprazole.[24]

We identified cystic dilation of fundic glands in 89% of the PPI-associated polyps studied. These polyps were generally small (<1 cm), and multiple polyps were often present. No correlation between number of polyps and dose of PPIs was observed, and *Helicobacter pylori* was not identified in any of the biopsy specimens. In a retrospective study of 6 omeprazole-associated polyps, Stolte and associates observed that the cystically dilated fundic glands were mostly lined with flattened parietal and chief cells but were, in 3 cases, also lined with foveolar epithelium, the lining commonly seen in hyperplastic polyps.[11] Hirt and colleagues suggests that specific histologic differences may exist between the sporadic fundic gland polyps classically described and those associated with PPI use.[25] Weinstein and associates reported that the PPI polyps were similar to those seen in Gardner's syndrome.[26] These authors observed that some of the glands in their series were almost exclusively lined with parietal cells. They also noted that the mucosa adjacent to the polyps exhibited an expanded parietal cell zone and parietal cell hyperplasia relative to the mucosa before institution of omeprazole.

In a related study, the same group demonstrated an expansion of the parietal zone, which they considered a precursor lesion to the development of fundic gland polyps.[26] We found no evidence of parietal cell hyperplasia, either by light or electron microscopy, in the PPI polyps studied. Instead, we report the combination, in the same patient, of both fundic-type and hyperplastic polyps in association with PPI treatment. In a provocative report, Roberts and associates described the development of hyperplastic gastric polyps in 4 of 41 patients receiving long-term (>12 months) alternate-day omeprazole therapy.[27] This group did not, however, clearly state whether these polyps contained hyperplasia of fundic glands. Moreover, the occurrence of both hyperplastic and fundic type polyps in the same patient receiving a PPI on a long-term basis has not, to our knowledge, been previously described in the English literature.

In conclusion, our results suggest that gastric polyps occur more frequently in PPI-treated patients than in the general population of individuals on whom endoscopies have been performed. Histologically, these polyps were of the fundic gland type, hyperplastic type, and inflammatory type, and they were histologically and ultrastructurally indistinguishable from the sporadically occurring polyps. They also lacked evidence of dysplasia. Because the long-term significance of these polyps is uncertain, prospective studies of their natural history are required.

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