Paolo Declich\textsuperscript{1}, Enrico Tavani\textsuperscript{1}, Aldo Ferrara\textsuperscript{2}, Stefano Caruso\textsuperscript{2}, Stefano Bellone\textsuperscript{1}

Sporadic Fundic Gland Polyps: Clinico-Pathologic Features and Associated Diseases

\textsuperscript{1}Service of Pathology, Rho Hospital, Italy,  
\textsuperscript{2}Division of Gastroenterology and Gastrointestinal Endoscopy, Legnano Hospital, Italy

Background. Fundic gland polyps have been described either in association with genetic polyposis syndromes of the colon, or in a sporadic form. In the first case they are diagnosed during family screening in asymptomatic subjects, while sporadic FGP patients often complain of upper gastrointestinal symptoms. So far, no great attention has been paid to the clinical presentation of these patients, so we undertook a clinico-pathologic study to further delineate: the clinical presentation at first examination; the associated gastrointestinal conditions; a possible role of omeprazole; \textit{Helicobacter pylori} (\textit{H pylori}) colonization, the presence of intestinal metaplasia and dysplasia.

Methods. We followed-up for a 9-year period with endoscopies a case series of 70 patients with sporadic FGPs, recording endoscopic data, symptoms, associated gastrointestinal conditions, previous therapies, histopathological findings. Results. The prevalence of the present series was 0.36%. The patient prevalence and number of polyps by age classes rose in women (maximum value in perimenopausal age), while was constant in males. We observed a frequent association between FGPs and esophageal conditions (34%), namely hiatus hernia-reflux esophagitis, significantly higher than in our endoscopic population (15%). Five patients had an isolated colonic adenoma. Only one patient had received long term omeprazole therapy. \textit{H pylori} was negative in all 70 FGPs, and in 15 samples of antral mucosa. No metaplastic or dysplastic lesions were seen. Conclusion. Sporadic FGP patients frequently complain of epigastric pain, burning, dyspepsia, probably related to the frequently associated esophageal pathology, namely reflux esophagitis-hiatus hernia (34%). Prevalence of FGPs and polyps number are linked to female sex (maximum rise for both values in perimenopausal age). No link with omeprazole therapy was seen. FGP patients appear to be protected from \textit{H pylori} colonization and ultimately from the development of intestinal metaplasia-dysplasia-gastric cancer. Nonetheless, they are apparently more prone to colonic adenomas. So, every sporadic FGP patient should undergo colonic surveillance.

Introduction

Fundic gland polyps (FGPs) are small, sessile (2–5 mm), usually multiple polyps of the gastric acid-secreting mucosa, described both in a sporadic form, prevalently in middle-aged females \cite{15}, and associated with familial adenomatous polyposis (FAP)-Gardner’s syndrome, in patients in the II–III decades of life, without a gender prevalence \cite{36}. FGPs have been described as commonly occurring lesions in patients with attenuated variants of FAP (AFAP) \cite{26, 28}, and recently even associated with the Zollinger-Ellison syndrome \cite{1, 5, 11}.

Whereas syndromic FGPs are diagnosed in asymptomatic subjects during the screening of FAP families \cite{13, 19}, sporadic FGPs are diagnosed in patients complaining of upper gastrointestinal symptoms \cite{19, 29}. Nonetheless, symptoms at first presentation have been rarely reported, without great detail, and only Sipponen et al. \cite{31} reported a detailed account of associated gastrointestinal lesions in their case series of sporadic FGPs.

Recently, after the paper by Graham \cite{17}, there has been great interest about a possible role of omeprazole into the genesis of FGPs, and other reports have been published on this highly controversial topic, either suggesting \cite{2, 16} or denying such association \cite{7, 34, 35}.

Moreover, recent studies have shown a very low prevalence of \textit{Helicobacter pylori} (\textit{H pylori}) colonization in sporadic FGPs patients, when compared to normal control subjects \cite{7, 8, 12, 30, 34, 38} opening a very interesting field for future research. Recently, Watanabe et al. \cite{37} described two rare patients that acquired \textit{H pylori} with reduction or disappearance of FGPs; we too, could recently observe an
additional patient [9], from a case series unrelated to the one reported.

We undertook a study of a case series of 70 patients with sporadic FGPs in order to evaluate: all available clinicopathological data, with particular attention to symptoms at first presentation and any gastrointestinal or extraintestinal associated lesions; the validation of a possible promoting role of the omeprazole treatment; the prevalence of \( H. pylori \) colonization, intestinal metaplasia, and dysplasia.

**Material and Methods**

During the period November 1988–December 1997, in 19,266 upper endoscopic examinations performed at the Division of Gastroenterology of Legnano Hospital, we found 70 patients with fundic gland polyps (FGPs). In all patients the endoscopic diagnosis was histologically confirmed. A negative family history of colon cancer was obtained in all patients; further, in 17 patients a colonoscopy or a barium enema were performed, negative for polyposis. The number of FGPs seen at first and subsequent endoscopic examinations was recorded, as well as age and symptoms at first presentation, all therapies before and during follow-up examinations, all associated intestinal and extraintestinal conditions at first examination and during the follow-up.

For statistical comparison, in the same study period, we recorded 2,908 patients with an esophageal condition (esophagitis-hiatus hernia).

At each endoscopic control FGPs were systematically biopsied. We evaluated the *Helicobacter pylori* (*H. pylori*) status on FGPs and surrounding mucosa, and for the last 15 patients even on a sample of antral mucosa.

With the aim to validate a possible role of the proton-pump inhibitors (omeprazole) into the genesis of FGPs, we studied a group of 24 patients (15 males, 9 females, male to female ratio of 1.6:1; mean age 46.2 years, range 22–66 years) suffering from reflux esophagitis. This group of patients was treated for at least 1 year with 20 mg/day of Omeprazole, and followed up for at least 2 years with endoscopy (mean number of examinations 3.7, range 2–10) studying the possible occurrence of the *de novo* FGPs [7].

We followed the previously described diagnostic criteria for FGPs [4, 25, 31] that are: cystic dilation of foveolae and body type glands, with intraluminal budding, shortened gastric pits, absent or negligible inflammation in the lamina propria. All the biopsies of FGPs and the 15 biopsies of antral mucosa were fixed in Bouin’s fixative and embedded in paraffin and 4 micron thick sections were stained with hematoxylin-eosin, Alcian blue (pH 2.5)-PAS, and Giemsa. For each sample were evaluated the presence or absence of \( H. pylori \), intestinal metaplasia, and dysplasia.

**Results**

**General data and prevalence**

During the study period, in 19,266 upper digestive examinations were identified 70 patients (prevalence of 0.36%) with fundic gland polyps (FGPs). The patients were 51 females and 19 males (females/males ratio of 2.7/1), with a mean age of 52 years (interval 24-87 years).

The prevalence of FGPs according to sex and age classes (Fig. 1) showed a steady rise in females with a peak in perimenopausal years, while in males it remained constant from 30 through 70 years.
Family history

Family history for colon carcinoma was negative for all 70 patients. Moreover, a barium enema or colonoscopy was performed in 17 patients (24%): 12 patients were negative (70%); in 5 patients, all aged over 55 years a unique colonic adenoma was diagnosed. All the 70 patients were considered bearers of sporadic FGPs.

Endoscopy

Endoscopic aspect was characterized in 69 out of 70 patients by small (2–5 mm) slightly elevated polyps in the body-fundus, varying in number from 1–2 to 10–20. They were covered by normally appearing pale pink glistening mucosa (Fig. 2). In one patient evaluated for hematemesis the gastric walls were covered by blood, and the biopsy diagnostic for FGP was blindly obtained. The number of polyps at first examination varied from 1 to 35 (mean 8.9). Stratifying the number of polyps recorded at first examination according to sex and age classes (Fig. 3), the number of polyps appeared again to rise, reaching a peak in perimenopausal women, while it remained constant in males.

Clinical presentation

Forty-two out of 70 patients (60%) presented at first endoscopy with symptoms (Table 1); 3 patients were first examined because of unexplained anemia and weight loss; for 25 patients symptoms at first presentation were not recorded.

TABLE 1
Patients’ symptoms or reason for examination at first endoscopy

<table>
<thead>
<tr>
<th>Symptoms at 1st examination</th>
<th>FEMALES</th>
<th>MALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>GE reflux</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Digestive tract hemorrhage</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Anemia from unknown cause</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 2. Endoscopic aspect of multiple tiny polyps, covered with pink glistening mucosa.

Fig. 3. Patients’ stratification by sex and age according to polyps number.
Therapy

For 7 patients we could not obtain data about preceding drug assumption; in only 9 out of 63 there was an assumption of gastrointestinal tract related drugs: 1 patient had received omeprazole (20 mg/day for 1 year) for severe reflux esophagitis two years before the diagnosis of FGPs.

On the other hand we followed-up 24 patients suffering from reflux esophagitis (15 males, 9 females, M/F ratio 1.6/1; average age 46.2 years, range 22–66 years) treated for 1 year with 20 mg/day of omeprazole. The patients were endoscopically followed-up from the start of therapy for 2 years with repeated accurate examinations (average number of gastrosopies 3.7, range 2–10), without observing any case of de novo FGPs in the interval period [7].

Associated gastrointestinal lesions (Table 2)

Among our 70 patients, 45% had an associated gastrointestinal lesion or condition; 24 patients had an associated esophageal lesion (35%) and 5 patients had an associated fundic heterotopia in duodenum.

On the other hand, the prevalence of esophageal lesions in our endoscopic population was of 2,980 out of 19,266 examination (15%), a prevalence significantly lower than in the FGP group (p<0.0001).

<table>
<thead>
<tr>
<th>Associated GI lesions or conditions</th>
<th>FEMALES</th>
<th>MALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Esophageal diverticulum</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Achalasia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal leiomyoma</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Esophageal carcinoma</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Fundic heterotopia in duodenum</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Gastric angiodysplasia</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Biliary reflux</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Colonic adenomas</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. 4. Low power view of a fundic gland polyp, with superficial (foveolar) and deep cystic dilations (4A). At higher magnification the mucous component of the cysts is evident (4B). HE. Magn. 4A 40×, 4B 200×.
Follow-up

The median follow-up period was of 56 months (1–108 months). During the study period, 4 patients died from pathologies unrelated to FGPs (1 patient died from lymphoblastic lymphoma; 1 from myocardial infarction; 1 from disseminated serous papillary ovarian cancer; 1 patient from esophageal cancer). There was not any association with gastric or colon cancer.

Histology

All 70 patients had at least one biopsy diagnostic for FGP (Fig. 4), that is the presence of foveolar and deep cystic dilations, shortened gastric pits, with absent or negligible inflammation in the lamina propria. All biopsies were negative for intestinal metaplasia, dysplasia, Helicobacter pylori (H pylori). The last 15 cases had even an antral control biopsy, negative for inflammation and H pylori. Five patients had small multiple protrusions, covered by normally appearing mucosa, in the first portion of the duodenum that resulted to be fundic gland heterotopia, without cystic dilations or inflammation.

Discussion

We diagnosed FGPs in 70 out of 19,266 upper GI examinations (prevalence of 0.36%). The family history for colonic carcinoma was negative in all patients; 17 patients had even a negative colonoscopy or barium enema (sporadic patients). Our prevalence is in keeping with that of the literature (0.21–0.36%) [8, 19, 31, 39] for sporadic FGPs. Only Marcial et al. [27] and Kinoshita et al. [23] reported higher values (0.8% and 1.9%, respectively). This rise in prevalence could be due to a better awareness of FGPs, with an enhanced sensibility of the endoscopist. For instance, Marcial and co-workers reported a unique FGP in 58% of their patients. Even Sipponen and co-workers [31, 32] reported an apparent rise in prevalence between two different periods (0.06% and 1.43%, respectively). We also reported previously [8] a prevalence of 0.21% for our first 24 patients compared to the 0.36% of the present study.

The prevalence of sporadic FGPs in middle-aged females has been constantly reported in the literature [8, 18, 25, 31] and our findings (mean age 52 years; females/males ratio of 2.7/1) are in keeping with those. Studying our present series we found two new findings: we observed an age-related rise in FGPs prevalence in females (peak between 40 and 60 years), while the prevalence in males remained constant from 30 through 70 years (Fig. 1); we also observed a rise of the number of polyps at 1st endoscopy in females (peak between 40 to 60 years), while it remained constant in males (Fig. 2). So, the gender apparently influenced both the prevalence and the mean number of polyps in sporadic FGPs patients.

As regard to symptoms at first presentation, epigastric pain (28/70) and dyspepsia (9/70) were the commonest complaints, whereas three patients were investigated for anemia, weight loss or search of primary malignancy. The tiny polyps themselves are unlikely the culprit of these symptoms. Conversely, we observed a strong association between FGPs and esophageal conditions (34%), namely hiatus hernia-reflux esophagitis. This association, yet unreported, probably explains the patients’ complaints, and suggests that mechanical disturbances may be involved into the genesis of the polyps.

Omeprazole has been linked to the genesis of FGPs by some authors [2, 16, 17], while others, and ourselves, found no relationship [7, 8, 12, 34, 35]. Many of the reported cases of the omeprazole-related FGPs were retrospectively studied in patients treated for hiatus hernia-reflux esophagitis. As we have found a frequent association, in our untreated patients, between FGPs and esophageal conditions, one could ask if the apparently de novo FGPs reported in the literature were not missed at first examination. We had among our 70 patients only one case previously treated with omeprazole for severe reflux esophagitis. On the other hand, none of our 24 patients treated with omeprazole for reflux esophagitis developed de novo FGPs [7].

Relevant to this point, a recently described lesion, the parietal cell hyperplasia (PCH), has been linked to omeprazole treatment [34, 33, 24]. It is characterized by an augmented number of parietal cells that protrude into the gland lumen giving them a “serrated contour”. Glands may exhibit even some cystic dilations [4]; the distinguishing feature against FGPs being the absence of superficial dilations lined by mucous cells [33, 34]. Admittedly, ambiguous borderline cases exist [33, 34]: we have seen recently one case with histological features consistent both with PCH and FGP [4]. So, PCH should be seriously considered in the differential diagnosis with FGPs in patients treated with omeprazole.

Five out of 17 patients (29.4%) in whom a colonoscopy or a barium enema were performed had a unique colonic adenoma. The number of patients is low, but our data suggest that even patients with sporadic FGPs may have an increased risk of simultaneous colonic adenomas, as previously shown in a very large case series [14], when compared with the expected prevalence in general asymptomatic population under screening (2.3–12.3%) [3]. Recently Jung et al. [22] confirmed these same results in a prospective study, even if they do not fully selected their cases as sporadic.

As regard to Helicobacter pylori (H pylori) prevalence, we could observe no case of H pylori colonization, neither on the polyp surface, nor on the antral biopsies taken.
in 15 patients with FGPs. Our data are consistent with the reported absence or rarity of *H pylori* in sporadic FGPs patients [7, 9, 12, 34]. Along with the absence of *H pylori*, we could not observe any case of FGPs with intestinal metaplasia or dysplasia.

**Conclusions**

Sporadic FGPs are diagnosed in patients frequently complaining of upper gastrointestinal symptoms, probably related to a frequent albeit so far not reported associated esophageal pathology. A role of omeprazole into the genesis of FGPs has been suggested, but further prospective studies on larger case series are needed to validate this hypothesis. Patients with sporadic FGPs for yet unknown cause(s), appear resistant to *H pylori* colonization [9] and associated gastritis, intestinal metaplasia and dysplasia. Thus, patients with sporadic FGPs seem ultimately to be protected against high grade dysplasia, a very rarely reported association [21] and gastric cancer, never reported so far. Nonetheless they have an augmented risk of colonic adenomas [14, 22]. Thus even sporadic FGP patients need ideally a thorough study of the colon.

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**References**


Address for correspondence and reprint requests to:
Dr. Paolo Declich
Service of Pathology
Rho Hospital
Corso Europa n. 250
I-20017 Rho
Italy
Phone: 02-994303242
Fax: 02-994302742
Email: paolo.declich@libero.it