Abstract. Background: Fundic gland polyps (FGPs) are common hamartomatous cystic lesions in the gastric mucosa. The aim was to assess the cellular components in sections stained with Giemsa or toluidine blue: two stains that easily differentiate parietal from chief cells. Materials and Methods: Sixty-eight consecutive gastric biopsies having well-oriented sections from the fundic mucosa were investigated: 34 had FGP, and 34 were control cases. Using an ocular microscale, the thickness of each FGP was divided into an upper and a lower compartment. The proportion of parietal and chief cells in each compartment was assessed in 3 consecutive high power fields (×40).

Results: In FGPs, parietal cells predominated in the upper compartment where the parietal chief cell ratio ≥60 was 59.8%, and in the lower compartment it was only 5.9% (p<0.05). Within cysts, cell exfoliation with secondary eosinophilic nuclear-free material was found. FGPs also displayed small glandular islands with an admixture of parietal and chief cells. The cytoplasm of parietal cells was often ballooned, vacuolated, with basophilic deposits or anucleated (ghost cells). Conclusion: FGPs are composed of parietal cells predominantly in the upper half and with chief cells in the lower half, as well as with glandular islands showing cytological alterations in parietal cells. Intraluminal nuclear-free material seems to obstruct the outlets of the glands leading to cystic formation.

Fundic gland polyps (FGP) are small (≤5 mm), asymptomatic mucosal lumps that are incidentally disclosed at gastroscopic examinations performed for unrelated symptoms of the upper digestive tract or in gastric check-ups in patients with familial adenomatous polyposis (FAP) (1, 2). FGPs are the most common gastric lesion in patients with FAP, with a reported prevalence of between 0.04% to 11.1%, and in relation to other gastric polyps between 3% and 77% (3, 4). In recent years, much interest has centered on the risk of proton pump inhibitor (PPI) medication in the development of FGP (5-7). Several reports indicate that the prevalence of FGP is increased in patients receiving PPI. When high doses of PPI are administered for long periods of time, massive fundic gland polyposis may occur (8).

Sections from the normal fundic mucosa stained with hematoxylin and eosin (H&E) reveal triangular parietal cells with a centrally located nucleus and an eosinophilic cytoplasm (9) in the upper portion of the glands and cuboidal chief cells with a pale blue-gray (amphophilic) cytoplasm and a basally located nucleus in the lower portion. Despite differences in morphology and in topographic localization, a bona fide discrimination between all parietal cells and chief cells is, however, not straightforward in sections stained with H&E in man (10), although it is easily revealed in non-human primates (11). This limitation has probably hampered a closer study of the two main cell populations that FGPs are composed of in humans.

Searching for Helicobacter pylori, we recently found that both parietal and chief cells could easily be discriminated using modified Giemsa or toluidine blue stains (10, 12). This discrimination was not possible in sections stained with H&E. The purpose of the present work was to scrutinize the parietal cell and chief cell distributions in sections from FGPs stained with these two histochemical methods. Results were compared to those obtained in sections from the gastric corpus having either normal mucosa or chronic gastritis.

Materials and Methods

Sixty-eight consecutive gastric biopsies having well-oriented sections from the fundic mucosa were investigated: 34 had an FGP, and 34 were control cases. In control cases, 26 had normal mucosa (NM) and the remaining 8 chronic gastritis (CG) without focal or extensive atrophy or intestinal metaplasia. The Regional Ethical Committee approved the study.

Sixty-eight sections were stained with H&E, 16 with modified Giemsa stain (5 FGPs, 4 CG and 7 NM) and 52 with toluidine blue stain (29 FGPs, 4 CG and 19 NM). Fifteen FGPs were also stained with periodic acid Schiff (PAS).
Using an ocular microscale, the thickness of each FGP was divided into an upper and a lower compartment. The proportion of parietal and chief cells in each compartment was assessed in 3 consecutive high power fields (HPFs) (×40).

In control cases, the fundic mucosa was divided into an upper parietal-cell domain and a lower chief-cell domain. The proportion of light blue-stained parietal and dark blue-stained chief cells in each compartment was assessed in 3 consecutive HPFs.

Statistical analysis. The Mann-Whitney test was used to compare differences between groups. Statistical significance was defined as \( p<0.05 \).

Results

Parietal cell/chief cell ratio in FGPs. A total of 204 HPFs were analyzed in the 34 FGPs. Results in Table I show that in 59.8\% (61/102) of the HPF investigated in the upper compartment in the 34 FGP, the parietal chief cell ratio was ≥60, whereas in the lower compartment the proportion of FGPs with a parietal chief cell ratio ≥60 was only 5.9\% (6/102 HPF) \( (p<0.05) \). Thus, in FGPs, parietal cells were significantly more frequent in the upper half and chief cells in the lower half of the lesions.

Glandular anomalies in FGPs. In 94\% (32/34) of the FGPs the normal distribution of a parietal cell band on top and of a chief cell zone underneath was totally altered. Small glandular islands lined with a variable number of parietal cells, chief cells and occasionally mucus-producing cells (Figure 1) had replaced the normal glandular park (Figure 2). Isolated oxyntic glands were also found directly connected to the pits, without intercalated neck cells (Figure 3).

Table I. The parietal/chief cell ratio in 3 consecutive HPFs (×40), both in the upper and lower half of 34 fundic gland polyps (FGPs). FGPs were assessed in gastric sections by staining with modified Giemsa or toluidine blue. When using the same stains for the 34 controls, 26 had normal mucosa and 8 had chronic gastritis without atrophy or intestinal metaplasia

<table>
<thead>
<tr>
<th>Parietal chief cell ratio</th>
<th>Upper half</th>
<th>Lower half</th>
<th>Parietal cell compartment</th>
<th>Chief cell compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20</td>
<td>0</td>
<td>18 (17.6%)</td>
<td>0</td>
<td>102 (100%)</td>
</tr>
<tr>
<td>21–40</td>
<td>8 (7.8%)</td>
<td>35 (34.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>41–60</td>
<td>33 (32.4%)</td>
<td>43 (42.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>61–80</td>
<td>32 (31.4%)</td>
<td>6 (5.9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>81–100</td>
<td>29 (28.4%)</td>
<td>0</td>
<td>102 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>102 (100%)</td>
<td>102 (100%)</td>
<td>102(100%)</td>
<td>102 (100%)</td>
</tr>
</tbody>
</table>
Parietal cell abnormalities in FGPs. The cytoplasm in many parietal cells was ballooned (Figure 4), sometimes vacuolated, or without nucleus (ghost cells). Ring-shaped basophilic deposits could be discerned in the outer aspect of the cytoplasm (Figure 5). Luminal exfoliation (Figure 6) and cell-free plugs were also found (Figure 7).

Parietal chief cell ratio in NM and CG specimens. Sections from the gastric fundus with NM and with CG showed two distinct compartments: an upper parietal cell domain and a lower chief cell domain. In the former parietal cells predominated (≥96%) and in the latter zone chief cells predominated (≥93%) (Table I).

Discussion

FGPs have traditionally been regarded as non-neoplastic, possibly hamartomatous or hyperplastic/functional polyps (13). The presence of small glandular islands with an admixture of parietal and chief cells, as well as the occurrence of smooth muscle (14), should fulfil the criteria for a hamartomatous lesion.

Despite the relative high prevalence of FGP (1, 2) only few authors have investigated their histogenesis. According to Stemmerman (15), FGPs probably develop from the progressive dilation and infolding of glandular buds to produce irregular tortuous glands and microcysts. Odze et al. (14) claim that increased cell proliferation and subsequent differentiation of aberrant proliferative cells may explain the histogenesis of FGP, while Abraham et al. (16) claim that FGPs evolve through mutations of β-catenin.

In Giemsa and toluidine blue-stained sections, FGPs displayed apparently damaged parietal cells with ballooned cytoplasm, sometimes vacuolated, with ring-shaped basophilic deposits or lacking a nucleus (ghost cell). The increased cell proliferation in FGPs reported by some authors (3, 4), might mirror reparative cell proliferation generated by ongoing parietal cell breakdown. None of the gastric biopsies without FGPs had similar cellular aberrations.

Using H&E-stained sections, we recently found that in 86% of the FGPs (17), parietal cell exfoliation and/or plugs of anucleated structures with eosinophilic granules clogged the outlets of the glands. Thus, cellular alterations in parietal cells with luminal exfoliation and formation of eosinophilic debris (17) might lead to clogging of the outlet of the glands,
retention of natural glandular secretions and eventually to microcyst formation in FGP.

A further anomaly is that lysozyme (an innate antibacterial enzyme) is up-regulated in the epithelium covering FGP (18). The increased lysozyme production in these polyps (18) offers a plausible explanation for the absence of *Helicobacter pylori* infection in such patients (19, 20).

The finding of cellular aberrations in FGP is perhaps not surprising considering that genetic mutations are often recorded in hereditary traits, in the adenomatous polyposis coli gene (*APC*), and in sporadic in β-catenin, a downstream target regulated by the APC protein (21, 22). A common APC/β−catenin pathway seems to be involved in development of FGPs through the targeting of different genes, both in FAP and in sporadic cases.

The gene *ATP4A* encodes the H^+^/K^+^ ATPase, which is the major membrane constituent of parietal cells (23). Recent studies on genetically manipulated mice (24) showed that mice lacking H^+^/K^+^ ATPase (*Atp4a(−/−)* mice), developed countless, confluent glandular cysts in the fundic mucosa. The parietal cells in these knock-out *Atp4a(−/−)* mice were affected and much eosinophilic material (probably resulting from exfoliated parietal cells) was seen within the cysts. In time, these animals developed severe achlorhydria (23).

In conclusion, FGP are common hamartomatous lesions comprising parietal cells predominantly in the upper half and with chief cells in the lower half, as well as having glandular islands displaying cytological alterations in parietal cells. Intraluminal nuclear-free material seems to generate cystic formation by clogging the outlets of the glands.

References


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