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Immunophenotype of sporadic and familial adenomatous polyposis associated fundic gland polyps: a mucin and MIB1 study

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Background Fundic Gland Polyps (FGPs) are small sessile (2–5 mm) usually multiple polyps arising in the gastric, acid-secreting mucosa, described both in a sporadic form, prevalently in middle aged females, and associated with familial adenomatosis coli (FAP)-Gardner's syndrome and their attenuated variants (syndromic form). Aims We performed an immunohistochemical study on 5 syndromic (4 cases without and 1 case with dysplasia) and 28 sporadic FGPs, using monoclonal antibodies (MoAbs) against normal epitopes of fundic mucosa (Ck20, the surface gastric mucin M1, EMA, ChA), *H. pylori* and HLA-DR(Ia) antigens, CEA and mucin epitopes, and the Ki67 (MIB1) proliferation antigen, in order to establish the immunophenotype of FGPs; find any possible differences between sporadic and syndromic polyps. Results Ck20 and M1 were positive on surface and foveolar epithelium of controls, whereas sporadic and syndromic FGPs showed an enhanced deep positivity below foveolar necks ("foveolar metaplasia"); EMA was strongly positive on parietal cells, highlighting intracytoplasmic canaliculi. Chromogranin-positive cells in FGPs were alike controls, except for a sporadic case with micronodular hyperplasia. Ck7, as expected, was negative in controls, whereas the 5 syndromic FGPs and 25 of 28 sporadic FGPs showed a diffuse superficial and deep expression. *H pylori* antiserum gave negative results on all cases, and only 3 sporadic FGPs showed epithelial expression of HLA-DR(Ia). Syndromic FGPs were CEA negative, whereas 32% of sporadic FGPs expressed it. FGPs showed a neoexpression of the mucin oncofetal epitopes syalil-Tn (3/5 syndromic, 82% sporadic) CA19.9 and CA50 (4/5 syndromic, 14% sporadic). MIB1-labelling index of surface (30.5%) and deep (37.1%) compartments of the 4 syndromic FGPs without dysplasia was enhanced, with high statistical significance ($p<0.0001$) both in comparison to controls (16.9% superficial stain only) and sporadic FGPs (15.8% surface, 19.5% deep labeling indexes). Moreover, the MIB1 labeling-index of the syndromic case with dysplasia (60.8% surface, 56.6% deep labeling indexes) was further enhanced in comparison with the other 2 syndromic cases. Conclusions Sporadic and syndromic FGPs showed a neoexpression of Ck7, CEA, and mucin epitopes. As these markers are normal antigens of fetal stomach, FGPs showed a fetal, "immature" immunophenotype. The only difference we found between syndromic and sporadic polyps was a statistically significant enhanced MIB1-labelling index expression by syndromic FGPs, further enhanced in the syndromic FGP with dysplasia.

Introduction

Fundic gland polyps (FGPs) are small (2–5 mm) multiple sessile polyps of the acid-secreting gastric mucosa. They have been described both in a sporadic form, prevalently in a middle-aged female population [9] and in a syndromic form, associated with familial adenomatous polyposis (FAP)-Gardner's syndrome [29] and with attenuated familial adenomatous polyposis (AFAP) [14, 15].

Whatever the clinical setting, the histological picture of the FGPs, characterized by cystically dilated tortuous foveolae and glands, shortened gastric pits, absent to negligible inflammation in the lamina propria, absence of intestinal metaplasia, and absence or rarity of *Helicobacter pylori* colonization [3, 8, 20, 22, 23, 31] is the same in both the sporadic and the syndromic forms.

Even histochemical studies did not show consistent differences between sporadic and syndromic FGPs: earlier claims by Nishiura et al [16] that FAP-associated FGPs express *O*-acylated sialic acid were not subsequently confirmed [13, 17]. Only recently, Abraham and coworkers using molecular techniques could find a different spectrum of somatic mutations between sporadic and syndromic FGPs [1, 27].

We undertook a comparative study of the antigenic profile of sporadic and FAP-associated FGPs, with the aim to: establish the immunophenotype of FGPs; show possible qualitative or quantitative differences between sporadic and syndromic polyps.

Materials and Methods

From September 1997 to March 1999 we prospectively followed up 31 new patients bearing FGPs. Twenty eight patients had a negative family history for colonic carcinoma as well as a negative coloscopy or barium enema (**sporadic** FGPs).

Two siblings (21 and 29 years) from a family with familial adenomatous polyposis (FAP) and a third 21-year old female patient from an unrelated family, were on endoscopic follow-up after prophylactic total colectomy.

A 37 year old patient with a genetic defect on APC gene (deletion in heterozygosis of nucleotide in position 477, with the creation of a termination signal in the translation of codon 159 **[477delC(ter159)]**) consistent with an attenuated form of FAP (AFAP) was on coloscopic and upper endoscopic follow-up at the Legnano Hospital (the proband, father of our patient, died in 1998 of colonic adenocarcinoma at the age of 74 years; no FGPs were present).

An 18-year old male from a FAP family was selected from the pathologic files of the Imunologia Molecular da Universidade do Porto (IPATIMUP), Medical Faculty, Porto, Portugal (FC). As a whole we studied 5 patients with **syndromic** FGPs.

Endoscopic aspects, symptoms at first presentation, previous therapies and all associated gastrointestinal lesions other than polyps were accurately recorded in all patients.

We followed the previously described diagnostic criteria for FGPs [3, 13, 21] that is: shortened gastric pits, cystic dilations of both foveolae and body-type glands, with intraluminal budding, a lamina propria devoid of significant inflammation.

All biopsies of FGPs were fixed in Bouin, paraffin embedded and cut at 3 μm; the resection specimen of the third syndromic case was fixed in 10% formalin, embedded in paraffin and cut at 4 μm. All slides were stained with Hematoxylin-eosin, Giemsa and Alcian blue (pH 2.5)-PAS.

Immunohistochemistry

Further sections of the biopsies of the 4 syndromic cases, two representative sections of the gastrectomy specimen from the 5th syndromic case, biopsies of 28 sporadic FGPs and 4 control biopsies of histologically normal, *Helicobacter pylori* (*H. pylori*)-negative fundic mucosa, were obtained for the immunohistochemical study, using the antibodies listed in Table 1. All the immunohistochemical stains were done with the automated device LV1–1 LAB VISION-AUTOSTAINER (Lab Vision, Freemont, CA). Enzymatic digestion (pronase for 10' at room temperature) was used for anti-*H. pylori,* Ck7,

TABLE 1
Monoclonal antibodies used, with working time and dilutions

Antigen	Antibody	Pretreatments	Dilution	Time	Purchaser
H pylori	policlonal antiserum	proteinase K	1/10	50'	BioOptica
Ck 7	OV-T 12/30	proteinase K	1/50	45'	Dako
Ck20	Ks 20.8	proteinase K	1/20	45'	Dako
EMA	E29	none	1/50	50'	Dako
ChA	LK2H10+PHE5	none	1/100	45'	NeoMarkers
CEA	A5B7	proteinase K	1/20	60'	Dako
M1	45M1	none	1/100	45'	NeoMarkers
sialyl-Tn	B72.3	none	1/100	45'	NeoMarkers
CA19.9	116.NS-19.9	none	1/50	45'	Dako
CA50	C50:8:2:4	microwave oven*	prediluted	45'	Ylem
Ki-67	MIB 1	microwave oven**	1/50	60'	Ylem

*Treatment for 5' at 500 W, for 5' at 650 W in citrate buffer pH6;
**Treatment for 5' at 650 W, twice, in citrate buffer pH6.

Ck20 and CEA, whereas for CA50 and Ki–67 the slides were pretreated with a microwave oven, then cooled for 20' at room temperature. The study was performed using the ABC technique [11]. All primary antibodies, diluted in PBS were incubated at room temperature, secondary biotinilated antibodies, and AB-peroxidase, available in kits (HRP-Stravigen Multilink, Biogenex, San Ramon, CA). Diaminobenzidine (Biogenex) was used as chromogen. In each test, appropriate positive (a gastric biopsy with active chronic gastritis for the *H. pylori* antiserum, a normal gastric biopsy for M1, a colonic adenocarcinoma for Ck20, CEA, CA19.9, CA50; a breast cancer for EMA, Ck7, MIB1; a secretive endometrium for syalil-Tn; a normal lymphnode for HLA-DR(Ia); an appendicular carcinoid tumor for Ch A) and negative controls (omission of the primary antibody) were used. The immunohistochemical results, for antigens not normally expressed by control mucosa (Ck7, CEA, sialyl-Tn, CA19.9, CA50), were evaluated as follows:

N : completely negative;
-/+ : focal positivity, limited to occasional cells;
+ : diffuse positivity limited to the surface epithelium;
++ : diffuse positivity to the surface epithelium with focal deep (glandular) positivity;
+++ : diffuse positivity to the surface and deep (glandular) epithelium.

For antigens normally expressed by fundic mucosa the positivity was evaluated as preserved (+), reduced (-/+) or increased (++ or +++).

Counting method for the MIB1 labeling-index has been already described elsewhere [3]. Briefly, we determined the labeling index of 4 control biopsies, 5 syndromic and 28 sporadic FGPs. A separate evaluation was done for the surface-foveolar epithelium above the foveolar neck and the deep glands or cysts, in which at least one positive cell was present. Only brown stained nuclei were considered MIB1 positive. As a whole, more than 500 cells per compartment were counted. Differences in the MIB1 labeling-index of the superficial and deep glandular compartments between controls, sporadic and syndromic polyps, syndromic FGPs with or without dysplasia were statistically evaluated with the Student's t-test, using the MedCalc© statistical software (Mariakerke, Belgium). The results were considered significant when $p<0.05$.

Results

Clinical and Endoscopic findings

In the study period, in our Institution, on 3858 upper endoscopic examinations, 31 patients with fundic glands polyps (FGPs) were diagnosed. Twenty eight patients (average age of 57.8 years, female to male ratio of 2.1/1) had a negative family history for colon carcinoma as well as negative barium enemas or coloscopy. They were classified as sporadic FGPs, with a prevalence of 0.7%.

With regard to the clinical presentation of the 28 sporadic patients, all referred to endoscopic examination because of upper gastrointestinal symptoms (heartburn, epigastric pain, dyspepsia); 10 patients (3 of whom with previous therapy with omeprazole) had an associated esophageal pathology (2 hiatus hernia; 6 hiatus hernia+reflux esophagitis; 1 reflux esophagitis; 1 esophageal varices) and 4 had duodenal pathology (2 ulcers; 1 duodenitis; 1 fundic heterotopia). In the remaining 14 cases there was no relevant esophageal and duodenal pathology.

The FGPs were discovered in all 5 syndromic patients during follow-up examination. Our first three patients had underwent total colectomy, and developed mild to moderate dysplasia of Vater papilla during the follow-up; the AFAP patient was in upper-endoscopic and coloscopic follow-up. He developed both an adenoma of Vater papilla with moderate dysplasia, and sparse right colonic adenomas (a total of 18 adenomas resected in 3 successive coloscopies) during the follow-up. The Portuguese patient had total gastrectomy for FGPs with severe dysplasia.

Endoscopically (Fig. 1A–B), sporadic FGPs were often multiple (5–20), sessile, minute (2–5 mm in diameter) polyps, covered by pink mucosa. They were exclusively limited to the corpus-fundic region, in a normal appearing background mucosa. In 1 patient the biopsy (with histology diagnostic for FGP) was taken on a slightly depressed fundic mucosa. Four of five syndromic patients presented hun-

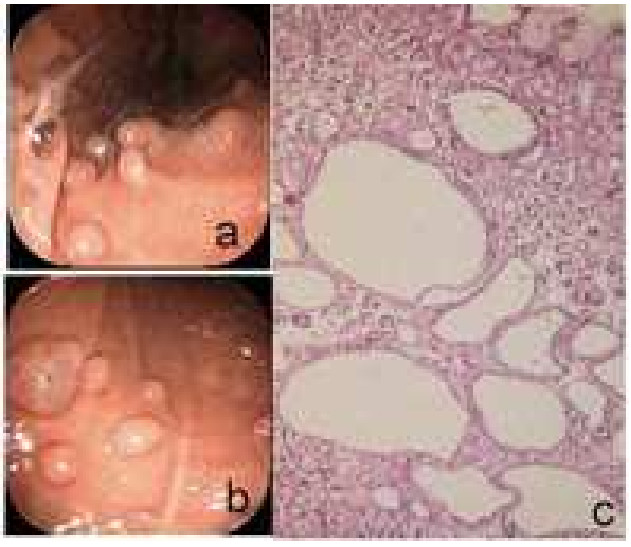

Fig. 1. Fundic gland polyps appear endoscopically as tiny sessile protrusions on a background of normal pink glistening mucosa (1a & b) and histologically show both foveolar and deep glandular dilations (1c).

TABLE 2
Immunohistochemical results

Controls	N	-/+	+	++	+++	Total
Antigen						
Ck20*	**-**	-	4	-	-	4
M1*	**-**	-	4	-	-	4
EMA	**-**	-	4	-	-	4
ChA	**-**	-	4	-	-	4
H pylori	**4**	-	-	-	-	4
HLA-DRII	**4**	-	-	-	-	4
Ck 7	**4**	-	-	-	-	4
CEA	**3**	1	-	-	-	4
sialyl-Tn	**1**	3	-	-	-	4
CA19.9	**3**	1	-	-	-	4
CA50	**2**	-	**2**	**-**	-	4

Sporadic FGPs	N	-/+	+	++	+++	Total
Antigen						
Ck20*			24	4		28
M1*			6	10	12	28
EMA			28			28
ChA			27		1§	28
H pylori	**28**					28
HLA-DRII	**25**		2	1		28
Ck 7	**1**	2		6	19	28
CEA	**15**	4	9			28
sialyl-Tn	**5**		17	6		28
CA19.9	**20**	4	1		3	28
CA50	**16**	5	**3**	**1**	3	28

Syndromic FGPs	N	-/+	+	++	+++	Total
Antigen						
Ck20*			1	4		5
M1*				1	4	5
EMA			5			5
ChA			5			5
H pylori	**5**					5
HLA-DRII	**5**					5
Ck 7					5	5
CEA	**4**	1				5
sialyl-Tn		3	2			5
CA19.9	**1**	1		1	2	5
CA50		2		**1**	2	5

§ nodular hyperplasia.

dreds of FGPs carpeting the body fundus mucosa. All 5 patients showed the mucosa overlying Vater papilla from slightly elevated and irregular to frankly polypoid.

During the follow-up (ranging from 6 to 24 months, with a median of 6 months), none of the patients developed a gastrointestinal neoplasia.

Histology

In all 32 patients, the criteria for the diagnosis of FGPs were met, that is foveolar-glandular dilations (Fig. 1C), with shortened gastric pits. At light microscopic level, mucous cells (predominant in foveolar cysts), eosinophilic parietal cells with sparse deeply basophilic chief cells (predominant in deep cysts) were easily distinguished. The lamina propria appeared consistently normal, occasionally with slight edema, without inflammatory infiltrate or smooth muscle fibers. The Alcian blue (pH 2.5)-PAS stain demonstrated focal complete intestinal metaplasia in one sporadic case.

The syndromic case with dysplasia showed residual areas characteristic of FGP intermingled with areas of incomplete intestinal metaplasia with moderate dysplasia. The search for *H. pylori* in FGPs on Giemsa stained sections was negative in all 32 FGPs. Moreover, in 9 patients a sample of normal appearing antral mucosa was taken together with FGPs. Antral biopsies were free from both *H. pylori* and inflammation, and Alcian blue-PAS stain showed no metaplastic change.

Immunohistochemistry (Table 2)

Antigens normally expressed by fundic mucosa- Ck20 and M1 (gastric surface mucin) positivity was restricted to surface epithelium-foveolar necks in controls, whereas FGPs showed a slight Ck20 (4/5 syndromic, 14% of sporadic) and a marked M1 (5/5 syndromic, 78.5% of sporadic) positivity below foveolar necks, highlighting the mucous component of cysts (Fig. 2A–B).

E 29 MoAb (against EMA) highlighted the parietal cells of the cysts in FGPs, with positivity of intracytoplasmic canaliculi [2].

PHE 5 and LK2H10 MoAbs against Chromogranin A [7] showed in controls 1–2 positive cells per glands. The 3 syndromic and 26 sporadic FGPs paralleled the normal distribution of endocrine cells; one sporadic case, with no previous therapies, presented micronodular hyperplasia.

Helicobacter pylori and HLA-DR(Ia) antigens

The 4 controls and all 32 FGPs resulted negative to the anti-*H. pylori* antiserum, confirming the light microscopic findings. LN3 MoAb, reacting against a non-polymorphic antigen of HLA-DR(Ia) region (29–33 kD), was constantly negative on epithelial cells of normal controls and the 3 syndromic cases; only 3 of 28 sporadic FGPs where positive.

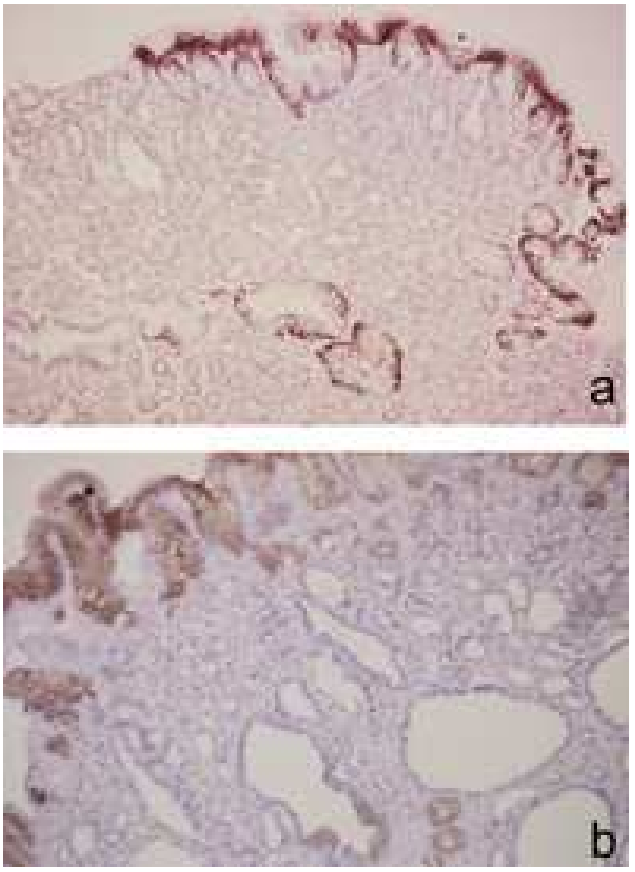

Fig. 2. Both CK20 (2a) and M1 (2b) show enhanced positivity below foveolar necks.

Cytokeratin 7

OV-T 12/30 MoAb against Ck7 resulted negative in all 4 controls. Conversely, it resulted diffusely positive, with superficial and deep distribution, in the 5 syndromic and in 25 of 28 sporadic cases (Fig. 3A–B).

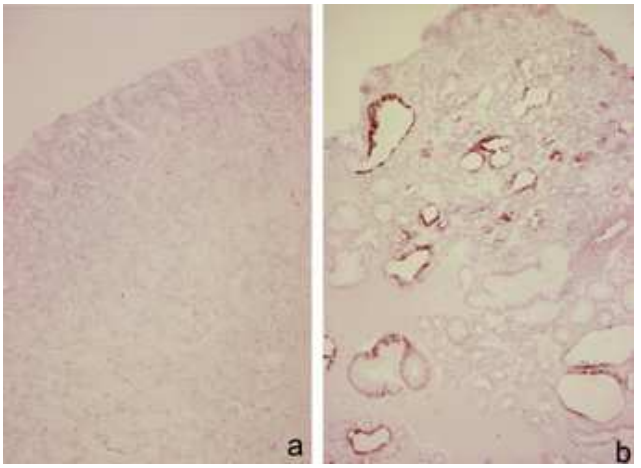

Fig. 3. Whereas normal control (3a) is negative, CK7 shows surface and deep positivity in a FGP (3b).

Oncofetal antigens

3 controls were negative, 1 only focally positive when stained with A5B7 MoAb (against a non-cross reacting epitope of CEA). The 4 syndromic FGPs without dysplasia were negative, whereas the syndromic FGP with dysplasia showed slight positivity limited to the dysplastic areas; 9 of 28 sporadic FGPs showed a diffuse surface positivity.

B72.3 MoAb (against the cancer-associated mucin epitope sialyl-Tn) was negative in the 4 controls. The 5 syndromic cases and 24 of 28 sporadic cases were positive.

The 4 controls were negative for CA19.19 and CA50 antigens, whereas 3/5 syndromic cases and 15% of sporadic FGPs where positive.

MIB1 labeling-index

MIB1 positivity in controls was limited to foveolar neck cells, with a labeling-index of 16.9%, without labeling of deep glandular compartment. On the other hand, all FGPs (19.5% sporadic FGPs, 37.1% the 4 syndromic FGPs without dysplasia) showed a deep staining below normal replicative neck zone (Fig. 4A–B). Comparison between surface MIB1-labeling index of controls and sporadic FGPs showed no statistical differences (16.9% VS 15.8%), whereas the 4 syndromic FGPs without dysplasia showed a surface (30.5%) and deep (37.1%) enhanced MIB1-labelling indexes, with high statistical significance ($p<0.0001$), both in comparison to controls (surface labeling) and sporadic FGPs (surface and deep labeling) (Fig. 4A and 4B). The syndromic case with dysplasia showed further enhanced surface (60.8%) and deep (56.6%) labeling indexes, again a difference statistically highly significant ($p<0.0001$) in comparison to sporadic and syndromic cases without dysplasia (Fig. 5).

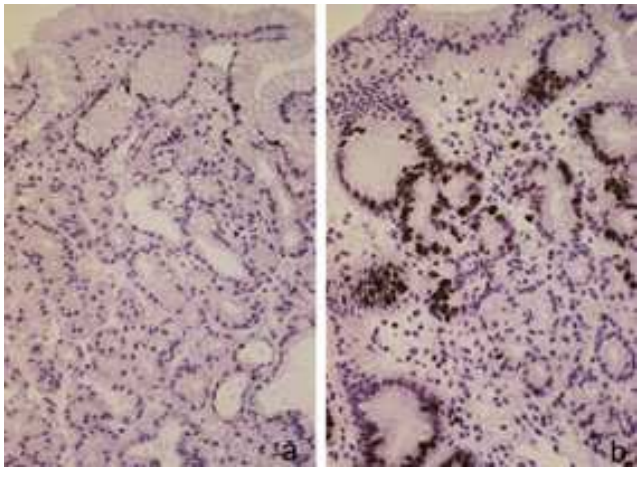

Fig. 4. The picture shows the MIB1 staining in a sporadic (4a) and in a syndromic (4b) polyp.

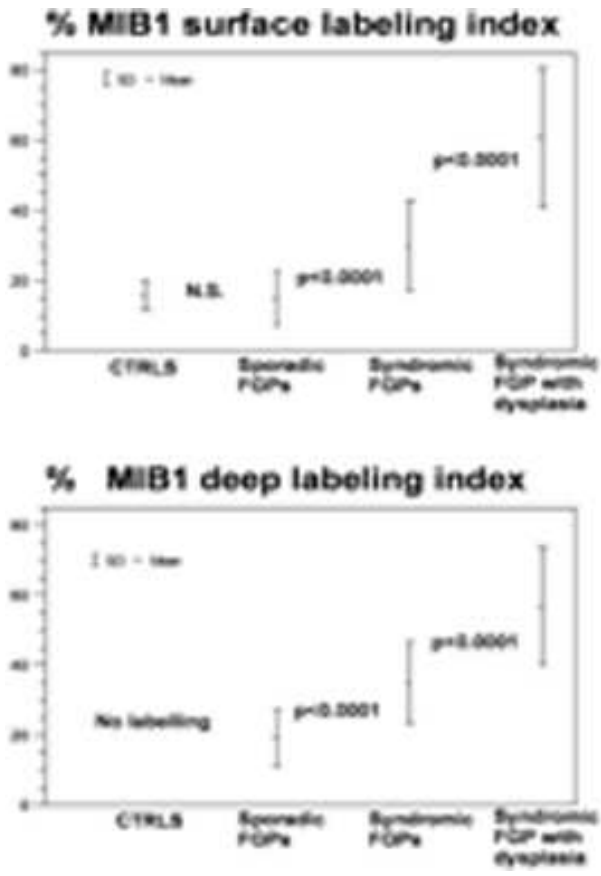

Fig. 5. MIB1 labeling index in controls, sporadic and syndromic polyps.

Discussion

Fundic gland polyps have been independently described both in a sporadic form prevalently in middle-aged females [9], in association with familial adenomatous polyposis [29] and attenuated variants [14], in the II–III decades of life without gender prevalence. Whatever the clinical setting, the histology of FGPs is the same. In an elegant morphometric study, Odze et al [17] could not find even subtle histological differences. Nishiura et al. [16] claimed that syndromic FGPs expressed *O*-acylated sialomucins, a statement that has been subsequently disproved by two other independent studies [13, 17].

Only using molecular techniques, Abraham and coworkers could find a different spectrum of somatic mutations between sporadic and syndromic FGPs [1, 27].

Here we studied both the clinico-endoscopic findings and the immunophenotype of a case series of 28 sporadic and 5 syndromic FGPs, with the aim to find possible differences between the two groups.

From the clinical point of view, we confirmed on a different group of patients the frequent association (35.7%) between sporadic FGPs and esophageal pathology (namely

hiatus hernia-reflux esophagitis). We have already reported that sporadic FGPs are often associated with esophageal pathology [6].

As regard to the number of polyps seen at endoscopy, we found hundreds of polyps in our 5 syndromic patients, compared to 1–20 polyps in the sporadic patients. Earlier studies [16] found the same finding, whereas others denied it [13]. Though our experience is based only on 5 patients, our findings seem to confirm a different endoscopical presentation, and it seems at least prudent to study with additional examination every patient with a disproportionate number of FGPs.

The immunophenotyping of FGPs showed in both sporadic (78.5%) and syndromic (5/5) polyps a deep expansion below foveolar necks of the gastric surface mucin M1 positivity. This process of "foveolar metaplasia" [19] seems characteristic of FGPs [4]. All other markers of normal body-fundus mucosa showed positivity in FGPs like controls.

The stain with *H. pylori* antiserum confirmed the negativity, already seen with conventional Giemsa stain in all 31 polyps and in the 9 samples of antral mucosa. In keeping with this result, only 3 sporadic FGPs (10%), showed an epithelial expression of HLA-DR(Ia). It has been already shown [30] that hyperplastic polyps frequently (75%) show an epithelial expression of HLA-DR(Ia), in relationship with the frequent *H. pylori* colonization, whereas FGPs rarely expressed this antigen (8%).

Cytokeratin 7 is not expressed by normal adult gastric mucosa [28], whereas is expressed by fetal stomach [12,24] and rarely, in chronic atrophic autoimmune gastritis [25] or, transitory, during gastric carcinogenesis [26]. Even gastric incomplete intestinal metaplasia shows only weak focal positivity [18]. Surprisingly, Ck7 was frequently expressed by all syndromic FGPs and by 89.2% of sporadic cases [5].

With the exception of CEA, negative in all 5 syndromic cases, the oncofetal mucin epitopes Sialyl-Tn, sialyl-Lewis b (CA19.9) and sialyl-fucosil-lactotetraose (CA50) were all frequently expressed in both sporadic and syndromic FGPs.

We would tentatively explain this abnormal immunophenotype (Ck7+, CEA+, sialyl-Tn+, CA19.9+, CA50+) as an expression of "fetal", immature phenotype. In a previous immunohistochemical work, Japanese authors had demonstrated an expression of glicentin and glucagon by FGPs, being this molecules expressed by fetal stomach [10].

This fetal immunophenotype may be in turn related to the enhanced proliferation of FGPs. Sporadic FGPs showed a superficial MIB1 labeling index like controls (15–16%) but a downward proliferative activity (17–20%) that was absent in controls. Moreover, the 4 syndromic FGPs without dysplasia showed enhanced superficial (30.5%) and deep (37%) labeling indexes, with highly significant ($p<0.0001$) statistical difference. Furthermore the dysplastic FGP, when compared with the 4 other syndromic cases, showed a further increase of superficial (60.8%) and deep (56.6%) labeling indexes, again a highly significant ($p<0.0001$) statistical difference.

Thus only MIB1 labeling index shows a difference between sporadic and syndromic FGPs. As proliferation rises steadily (sporadic-syndromic without-syndromic with dysplasia), we suggest that enhanced proliferation may herald and immediately precede the development of overt dysplastic changes.

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