Gastric Polyp Growth during Endoscopic Surveillance for Esophageal Varices or Barrett's Esophagus

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ABSTRACT: **Background:** We recently observed patients with chronic liver disease (CLD) or chronic reflux symptoms (CRS) who developed gastric polyps (GPs) while undergoing surveillance gastroscopies for the detection of esophageal varices or Barrett's esophagus, respectively.

Objectives: To identify risk factors for GP growth and estimate its growth rate.

Methods: GP growth rate was defined as the number of days since the first gastroscopy (without polyps) in the surveillance program, until the gastroscopy when a GP was discovered.

Results: Gastric polyp growth rates in CLD and CRS patients were similar. However, hyperplastic gastric polyps (HGPs) were detected more often (87.5% vs. 60.5%, $P = 0.051$) and at a higher number (2.57 ± 1.33 vs. 1.65 ± 0.93, $P = 0.021$) in the CLD patients. Subgroup analysis revealed the following findings only in CLD patients with HGPs: (i) a positive correlation between the GP growth rate and the patient's age; the older the patient, the higher the GP growth rate ($r = 0.7$, $P = 0.004$). (ii) A negative correlation between the patient's age and the Ki-67 proliferation index value; the older the patient, the lower the Ki-67 value ($r = -0.64$, $P = 0.02$). No correlation was detected between Ki-67 values of HGPs in CLD patients and the presence of portal hypertension, infection with *Helicobacter pylori*, or proton pump inhibitor use.

Conclusions: In comparison with CRS patients, CLD patients developed HGPs more often and at a greater number. Young CLD patients may have a tendency to develop HGPs at a faster rate than elderly CLD patients.

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KEY WORDS: hyperplastic gastric polyp (HGP), fundic gland polyp (FGP), *Helicobacter pylori*, proton pump inhibitor (PPI), Ki-67, chronic liver disease (CLD)

Gastric polyps (GPs) are lesions that originate from the gastric epithelium and protrude into the gastric lumen. They are usually asymptomatic and in most patients are incidentally discovered during an esophagogastroduodenoscopy (EGD). With expanding indications for EGD, GPs are being encountered with increasing frequency [1,2]. Histologically, although there is a wide variety of GP types, the most prevalent are hyperplastic gastric polyp (HGP) and fundic gland polyp (FGP) [1-4]. The pathogenesis of HGPs and FGPs is poorly understood; however, it is believed to be a multifactorial process that includes chronic gastric mucosal injury from various etiologies, including infection with *Helicobacter pylori* and hypergastrinemia [5-10]. Infection with *H. pylori* is associated with mucosal injury and inflammation, as well as epithelial healing with an increase in epithelial cell turnover, regeneration and development of hyperplastic tissue that may persist and progress to the development of HGP [5,6]. Secondary hypergastrinemia caused by chronic *H. pylori* infection and/or chronic proton pump inhibitor (PPI) use has trophic effects on the gastric mucosa and may facilitate the growth of HGPs [5,6].

Following the widespread use of PPIs, a rise in the prevalence of FGPs has been documented [8-10]. It had been estimated that chronic PPI treatment (over 48 months) leads to a fivefold increase in the development of FGPs [7,8,11].

In a survey of 50,071 EGDs that were performed in our institution from 1994 to 2009, an increase in the GP prevalence was detected [12]. In patients with either chronic liver disease (CLD) or chronic reflux symptoms (CRS) who were undergoing surveillance EGD for the presence of either esophageal varices or Barrett's esophagus respectively, GP development was noticed during the study period. Based on these findings it was hypothesized that it would be possible to estimate the growth rate of GPs in CRS and CLD patients and to identify risk factors for GP growth.

PATIENTS AND METHODS

In our previous work [12] we retrospectively analyzed all pathologic material extracted from 50,071 EGDs that were performed at the Hadassah Medical Center in Jerusalem between January 1994 and December 2009. A database of demographic, clinical and pathologic data of 727 individuals found to have GPs was generated [12]. In the present work, we searched this database for patients with CLD or CRS who were discovered to have a GP while undergoing surveillance EGDs for the presence of either esophageal varices or Barrett's esophagus, respectively. Individuals who were found to have a GP during the surveillance program and had at least one previous EGD without a GP were selected for this study. The decision to perform the surveil-

lance program and the exact timing of the first and follow-up EGDs was made by the treating physician. At that time, no research was envisioned.

DATA COLLECTION

Data were collected from our database as well as from the patients' medical records, which included EGD reports and clinical summaries. Collected data include age, gender, race, medical background, chronic medications (including PPI usage in the period before the discovery of the GP), type of GP, chronic conditions for which EGD surveillance was performed, total number of EGDs performed during the surveillance, number and location of polyps revealed during the EGD, and *H. pylori* status (positive or negative).

The presence of *H. pylori* in the histologic specimens of the polyps or the surrounding gastric mucosa was detected using hematoxylin and eosin stains as well as Giemsa stains. After 2005, the presence of *H. pylori* in the gastric tissue was verified also by use of a peroxidase-conjugated monoclonal anti-*H. pylori* immunohistochemical stain (Dako, Glostup, Denmark). The presence of portal hypertension in CLD patients was determined by the presence of esophageal varices.

REVIEW OF HISTOPATHOLOGY

All pathology specimens (biopsy of the GP or the fully excised polyp) were reviewed by an expert gastrointestinal pathologist (O.P.). Histologic specimens with HGPs were evaluated for the presence of engorged and/or proliferating blood vessels, complex foveolar architecture, erosions and granulation tissue. These features were reported to be specific for GPs arising in patients with portal hypertension [13].

GASTRIC POLYP GROWTH RATE

The growth rate of a GP, i.e., the time it took for a polyp to develop, was reported as the number of days that elapsed from the first EGD of the surveillance program until the EGD when the GP was discovered.

KI-67 IMMUNOHISTOCHEMISTRY

Formalin-fixed paraffin-embedded tissue of each GP was sectioned at 4 µm. Deparafinized, rehydrated sections were subjected to the following procedures sequentially: retrieval in Nuclear Decloaker™ (Biocare Medical, USA) and staining in 3% peroxide and blocking in Background Buster™ (Innovex, USA). Monoclonal anti-human Ki-67 (Dako, Denmark) diluted 1:200 was applied overnight at 4°C. Antibodies were detected with ZytoChem™ plus HRP polymer anti-mouse (Zytomed, Germany) followed by diaminobenzidine tetrahydrochloride (DAB Chromogen System, Signet, Covance, UK) according to standard procedures. Sections were counterstained lightly with Mayer's hematoxylin and mounted in EUKITT.

KI-67 INDEX QUANTIFICATION

Digital photographs were obtained using an Olympus DP70 digital camera, mounted on a Zeiss Axioplan 2 optic microscope. Six to 10 digital photographs were obtained from each Ki-67-labeled slide (one slide per polyp) in order to include all microscopic fields. The ImmunoRatio plugin [14] of the ImageJ image analysis software (National Institutes of Health) [15] was used to quantify the Ki-67 index of each photograph. As recommended by the developers, the ImmunoRatio plugin was calibrated and validated with manual Ki-67 index quantification of a subset of cases (85 slides); the difference between manual and digital quantification was negligible (data not shown) [14].

STATISTICAL ANALYSIS

For all analyses a P value of 0.05 was considered statistically significant. Descriptive statistics were calculated for all demographic variables, as were variables concerning polyp types and the patients' medical history. The relationship between different groupings (such as polyp type and the presence or absence of CLD) and several other discrete variables was investigated with the help of chi-square tests. The relationship between different groupings (such as polyp type and the presence or absence of CLD) and several continuous variables was investigated with the help of analysis of variance (ANOVA). The relationship between several continuous variables was investigated with the help of Pearson correlation coefficients. Additionally, Fisher's exact test was performed where indicated. Kaplan-Meier curves, presenting the length of the individual GP growth rate, for all patients with HGPs from both the CRS and CLD groups were constructed.

ETHICS

This study was approved by the Hadassah Medical Center's ethics committee review board. In view of the legal requirement, Ki-67 proliferation index quantification on the GP tissues from any patient included in the study was performed only after informed consent from the patient or his/her legal representative was obtained.

RESULTS

Fifty-four patients were included in the study group. These patients were selected from our original cohort of 727 patients with gastric polyps. The demographics and clinical characteristics of the 54 patients are presented in Table 1. Except for HGPs and FGPs, no other polyp types were discovered in these patients. All the polyps were benign with no signs of epithelial dysplasia. These patients underwent an average of 3.7 EGDs (range 2–9) until discovery of the GP. Most of the patients had a prolonged PPI exposure and only a few harbored *H. pylori* within their gastric mucosa [Table 1].

Sixteen patients suffered from a variety of advanced CLD. These patients underwent surveillance EGDs to monitor for

the development of esophageal varices (6 patients) or to monitor the change in size of already known esophageal varices (10 patients). Thirty-eight patients underwent repeated EGDs for Barrett's esophagus surveillance. In order to understand the effects of CLD, the presence of portal hypertension, chronic PPI exposure and active *H. pylori* infection on gastric polyp formation, we further subdivided the study population into four subgroups: CRS patients with either FGPs or HGPs, and CLD patients with either FGPs or HGPs [Table 2]. HGPs were detected more often and at a higher number in the CLD than in the CRS patients (87.5% vs. 60.5%, $P = 0.051$ and 2.6 ± 1.3 *vs.* 1.6 ± 0.9, $P = 0.02$ respectively). *H. pylori* infection was present exclusively in the HGPs of patients from both groups. PPI exposure was more common in the CLD patients. Gender distribution, age at detection of the polyp, number of EGDs performed until detection of a GP and GP growth rate did not differ between the groups. Consent to perform Ki-67 proliferation index quantification was obtained from only 42 of the study group patients: 28 from the CRS group (9 with FGPs and 19 with HGPs) and 14 from the CLD group (2 with FGPs and 12 with HGPs). The Ki-67 index values were lower in the tissues of the FGPs. However, due to a wide variation in the Ki-67 index values in each group the differences were not significant [Table 2].

The distribution of GPs within the gastric cavity in the CRS patients and the CLD patients was similar. The histopathologic features that were previously reported to be characteristic for GP tissues arising in patients with portal hypertension [13] were detected in only a few of the CLD patients. Moreover, the reported characteristics were detected at a similar frequency in HGPs of both the CLD and the CRS patients.

In order to study the effect of CLD on the growth rate of HGPs, Kaplan-Meier curves, indicating the individual GP growth rate, for all patients with HGPs from the CRS and CLD groups were constructed. No difference between the curves for both groups was demonstrated [Figure 1]. Subgroup analysis of all patients with HGPs from the CRS and CLD groups revealed the following findings only in the CLD group:

- A positive correlation between the GP growth rate (in days) and the patient's age (in years); the older the patient the higher the GP growth rate ($r = 0.7$, $P = 0.004$) [Figure 2A]
- A negative correlation between the patient's age (in years) and the Ki-67 proliferation index value; the older the patient,

Table 1. Baseline demographic, endoscopic and clinical characteristics of the entire study population (n=54)

Baseline demographics of the entire study population (n=54)	
Age at detection of the polyp†	65.8 (9.8)
Female	61.1%
Jewish	96.3%
No. of EGDs performed until detection of the gastric polyp†	3.7 (1.7)
Patients with fundic gland polyp	31.5%
Patients with hyperplastic polyp	68.5%
Presence of *H. pylori* on histology	16.6%
History of prolonged PPI exposure	87.7%
Type of liver disease in patients from the liver disease group (n=16)	
Chronic hepatitis C	37.5%
Cryptogenic	18.7%
Non-alcoholic fatty liver disease	12.5%
Autoimmune hepatitis	12.5%
Chronic hepatitis B	12.5%
Primary biliary cirrhosis	6.3%

†Data in these rows is reported as mean (± SD)

EGD = esophagogastroduodenoscopy, *H. pylori* = *Helicobacter pylori*, PPI = proton pump inhibitor

Table 2. Baseline demographic and clinical characteristics of the four study subgroups

	Chronic reflux symptoms group (n=38)		**Chronic liver disease group (n=16)**		
Variable	**FGP patients (n=15)**	**HGP patients (n=23)**	**FGP patients (n=2)**	**HGP patients (n=14)**	***P* value**
Age at polyp detection†	65.2 (9.8)	67.4 (10.2)	70.5 (12.0)	63.4 (9.5)	0.59
No. of gastroscopies performed until gastric polyp detection†	4.0 (1.8)	3.4 (1.6)	4.5 (0.7)	3.8 (1.9)	0.70
No. of FGPs detected†	1.93 (0.67)		2.5 (2.1)		0.86
No. of HGPs detected†		1.6 (0.9)		2.6 (1.3)	0.02
Presence of *H. pylori* on histology	0%	25%	0%	23%	0.22
History of prolonged PPI exposure	100%	71.4%	100%	100%	0.03
Gastric polyp growth rate (days)†	2171 (1346)	1760 (1311)	2894 (2456)	1598 (1470)	0.49
Ki-67 index (% of labeled nuclei)†§	2.9 (2.8)	8.7 (10.1)	1.5 (0.5)	5.8 (4.7)	0.22

†Data in these rows presented as mean (± SD)

§Consent to perform Ki-67 index quantification was obtained from only 11 patients with FGPs and from 31 patients with HGPs (see "Ethics" paragraph in the Patients and Methods section and Results section for details)

FGP = fundic gland polyp, HGP = hyperplastic gastric polyp, PPI = proton pump inhibitor

the lower the Ki-67 value (r = -0.64, P = 0.02) [Figure 2B]

- No correlation between the Ki-67 proliferation index values and presence of portal hypertension, the patient's gender, the presence of *H. pylori* infection and exposure to PPI.

DISCUSSION

In recent years, benign gastric polyps such as FGPs and HGPs are being increasingly discovered during EGDs performed for various indications [12]. The rapid and dynamic changes in the epidemiology of gastric polyps have enabled us to identify risk factors for GP development and to estimate its growth rate. The mean value of the growth rate for either the HGPs or FGP ranged from 1598 to 2171 days, respectively. Growth rates for HGPs in the CLD patients correlated with age; the older the patient, the lower the proliferation of the GP mucosa and the higher the GP growth rate.

GP growth rate for HGPs were already reported in patients after bone marrow and solid organ transplantation [16,17]. In one study the median time (and range) for the discovery of the GP was 11 months after transplantation (range 3–28) [16]. In another study the average time for the discovery of the GP was 28 months [17]. Interestingly, some of the characteristics of the patients with CLD from the present study were also reported in the transplanted patients: in both groups the GPs tended to be multiple, to occur more often in younger patients, and were not associated with *H. pylori* infection [16,17]. The cause of the rapid growth of HGPs in these patients was not found. It was hypothesized that the immunosuppressive agents taken by the patients in the post-transplant period altered their gastric mucosal response to external insults [16].

Altered gastric mucosal response to injury may also be present in CLD patients with portal hypertensive gastropathy [18,19]. Portal hypertensive gastropathy is characterized by a complex of structural changes that occur through all the components of the gastric wall [18]. It has been suggested that the gastric mucosa in patients with portal gastropathy is more susceptible to injury because of mucosal hypoxia, impaired mucosal defense, impaired healing ability, and alteration in epithelial cell integrity [18,19].

Patients with cirrhosis of various etiologies have an increased risk for both hepatobiliary and various extra-hepatic malignancies [20]. None of the GPs from patients in the present study revealed any signs of dysplasia. Thus, it can be concluded that a premalignant process was not the cause of GP development in the patient population of this study. This finding is supported by the

Figure 1. Gastric polyp growth rate (in days from the first surveillance gastroscopy) for hyperplastic gastric polyps in patients with either chronic reflux symptoms (CRS) or chronic liver disease (CLD)

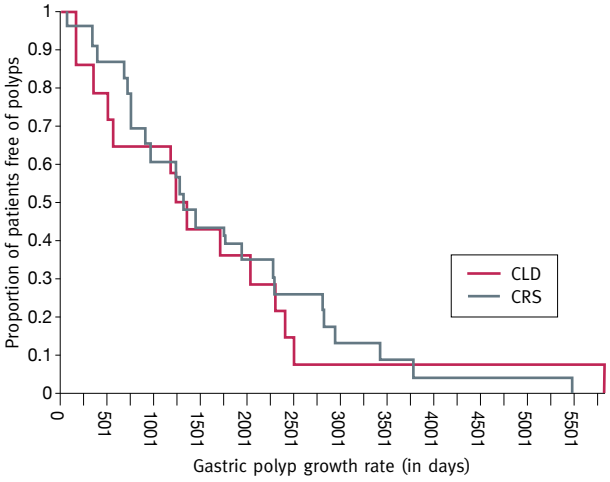
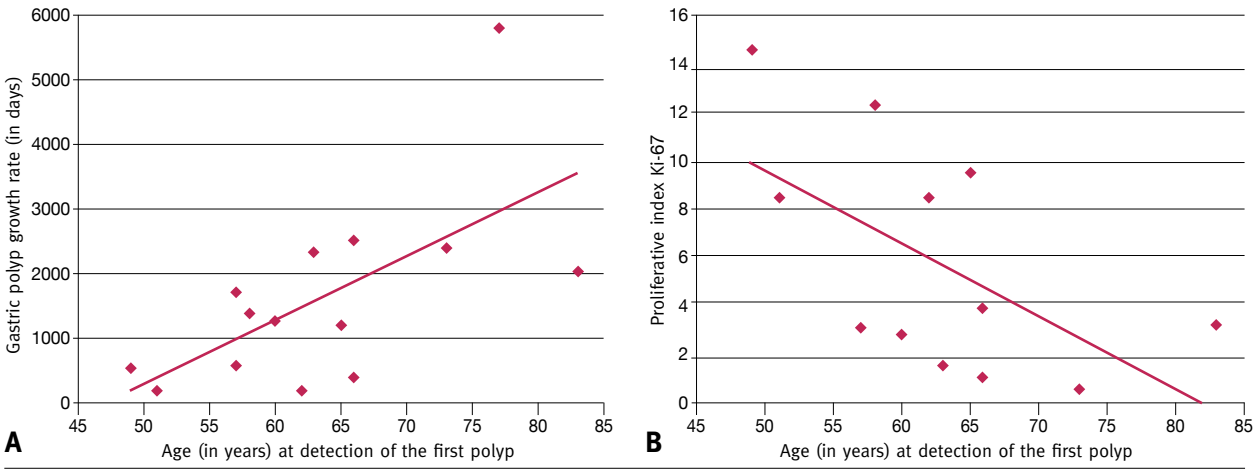


Figure 2. Correlation between the ages (in years) at the detection of the first polyp in the chronic liver disease patients with hyperplastic gastric polyp. **[A]** Gastric polyp growth rate (in days) (r = 0.7, P = 0.004), and **[B]** the value of the Ki-67 proliferation index (r = -0.64, P = 0.02). Consent to perform Ki-67 quantification was received only from 12 (of 14) patients in this group



lack of reports showing that cirrhosis of any etiology is associated with an increased risk of malignant epithelial gastric tumors [20].

In order to evaluate the relatively rapid growth rate of GPs in our study group, Ki-67 proliferation index staining of the GP mucosa was performed. The Ki-67 protein has been used extensively as a proliferation marker in several tissues, including gastric mucosa [21-23]. The mean value of the Ki-67 proliferation index found in patients with HGPs was higher than the value measured in patients with FGPs. Although the difference was not significant, such a difference is expected. The proliferative component of the HGPs is usually higher than observed in FGPs [23,24].

The present study yielded interesting findings regarding the growth rate of HGPs in CLD patients: growth rates were lower in younger patients and vice versa. Compatible with this finding was the observation that the Ki-67 proliferation index values were higher in younger CLD patients and vice versa. These changes may be attributed to age-related changes that occur in the gastric mucosa [25].

Our study has several limitations that should be mentioned:

- The selection of individuals with a GP was retrospective and as such was subjected to selection bias
- The retrospective nature of this study did not allow us to fully explore all events associated with the development and regression of GPs, such as starting PPI treatment or the eradication of *H. pylori* infection [1-12]
- Most of the CLD and CRS patients who underwent surveillance EGDs during the study period were not found to have a GP. The total number of individuals in each subgroup found to have a GP was small. Thus, the clinical relevance of our findings is not fully clear
- The repeated EGDs were not performed at regular intervals. This could hamper the detection of GPs and influence the calculation of the GP growth rate. However, as seen in Table 2, the number of repeat EGDs performed during the study period did not differ between the study subgroups.

Taking the above mentioned limitations into account it is suggested that until a larger prospective study validates our findings, its conclusions should be interpreted cautiously. Nevertheless, this study demonstrated that compared to CRS patients, CLD patients may tend to develop HGPs at a greater number and at a younger age. The increased growth rate of HGPs in this group of patients is probably related to yet unknown factors within the gastric mucosa, which are related to the presence of both advanced CLD and portal hypertension.

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