Original Article

Acquired Hyperplastic Gastric Polyps After Treatment of Ulcer

Wen-Hsiung Chang, Shou-Chuan Shih, Horng-Yuan Wang, Ching-Wei Chang, Chih-Jen Chen, Ming-Jen Chen*

Background/Purpose: Healing of gastric ulcers requires repair by epithelial migration and proliferation. We have found a small proportion of patients with acquired hyperplastic polyps at the healed ulcer site. The aim of this study was to identify clinical characteristics that might be associated with the development of hyperplastic polyps at the site of healed gastric ulcers.

Methods: This was a retrospective review of 86 patients with gastric ulcers from April 2006 to September 2008. After initial endoscopy, the patients were all treated with proton pump inhibitors, after which a second endoscopy was performed. Demographic data, polyp characteristics (endoscopic and histological), Helicobacter pylori status, and duration of treatment were analyzed.

Results: A total of 24 hyperplastic gastric polyps were found in 18 patients; all at the site of the healed ulcer (20 in the antrum and 4 in the corpus). The mean size of the ulcers prior to treatment was 14.5 ± 9.1 mm. Hyperplastic gastric polyps were more likely to occur at the site of ulcers larger than 10 mm (odds ratio = 9.57, 95% confidence interval = 2.50–36.65). Age, sex, H. pylori status, ulcer location and duration of treatment did not differ significantly between patients with and without polyps.

Conclusion: Hyperplastic polyps that develop after healing of gastric ulcers are likely to be extensive mucosal injury. A gastric ulcer larger than 10 mm is associated with a significantly increased risk of hyperplastic polyps.

Key Words: eradication, gastric ulcer, Helicobacter pylori, Hyperplastic polyps

Ulcer healing requires interaction between various tissues and cell types to achieve restoration of normal mucosal architecture. This active process is characterized by replacing the mucosal defect by accelerated cell migration and proliferation, which is supported by an important meshwork of connective tissue components. This process also requires close interaction between growth factors such as epidermal growth factor, transforming growth factor, and fibroblast growth factor, as well as cytokine-mediated signals to propel cells through the cell cycle or towards apoptosis.
Unlike polyps of the colon, gastric polyps are relatively uncommon, with an incidence of less than 2–3%. They can be non-neoplastic, such as hyperplastic polyps, or neoplastic, such as adenomas. Hyperplastic polyps are by far the most common histological type. They are usually less than 1 cm in length and are found primarily in the antrum and body of the stomach. The pathogenesis of hyperplastic polyps is not well understood, in contrast to gastric fundic gland polyps, which tend to arise in otherwise normal gastric mucosa.

Proton pump inhibitors (PPIs) are potent suppressors of gastric acid production, and they can also have a pH-independent effect on ulcer healing. Healing of gastric ulcers generally occurs within 8–12 weeks. We have noted the development of hyperplastic polyps at the site of healed gastric ulcers in a small proportion of patients treated with PPIs, but we have found little information in the literature to describe the natural history of hyperplastic polyps after treatment of gastric ulcers. We designed this study to investigate factors that might predispose to the development of hyperplastic polyps at the site of healed gastric ulcers.

Methods

Patients
We retrospectively reviewed the records of 2442 patients who underwent endoscopy by the same investigator (Dr M.J. Chen) at Mackay Memorial Hospital from April 2006 to September 2008. A total of 503 patients (20.6%) were diagnosed with gastric ulcer and 86 of those patients had undergone two endoscopic evaluations; one before and one after treatment. Of these 86 individuals, 18 were found to have gastric polyps at the site of the healed ulcers. The remaining 68 patients had healed ulcers but no polyps. After initial endoscopic diagnosis of a gastric ulcer, all patients were treated with 30 mg/day lansoprazole, with treatment continuing until the second endoscopy was performed. Patients with Helicobacter pylori infection upon initial endoscopy were treated with eradication therapy that consisted of 60 mg/day lansoprazole, 2 g/day amoxicillin, and 2 g/day tinidazole for 7 days at the beginning of the treatment period. All patients provided standard written informed consent as required by our institution for the endoscopic procedures, which included agreement for biopsies during the procedure when appropriate.

Demographic data, endoscopic and histological evaluation
Demographic data, duration of ulcer treatment, endoscopic findings (including size, number, and location of ulcers and polyps), and H. pylori status were extracted from the medical records. The size of ulcers and polyps had been recorded in the endoscopy report, with measurements made by open biopsy forceps. H. pylori infection was diagnosed on the basis of a positive rapid urease test (CLO test; Kimberly–Clark, Draper, UT, USA), or the finding of organisms by modified Giemsa stain in biopsy specimens. Hyperplastic gastric polyps were diagnosed by histopathological evaluation of the biopsy specimen, which showed elongation, twisting, and cystic dilatation of the foveolae. A further biopsy specimen was taken from the surrounding mucosa of hyperplastic polyps for histopathological comparison.

Endoscopic and histological follow-up of hyperplastic polyps
A third endoscopy to follow the hyperplastic polyps was performed in eight patients. The size and pattern of polyps were reviewed by comparing photographs from each endoscopy. At follow-up, the polyp size was assessed as having changed (> 10% smaller or larger) or not. Two investigators independently assessed each set of images. Disagreements were resolved by joint discussion to reach a consensus. Biopsies were repeated at each subsequent endoscopy to ensure that the polyps were indeed hyperplastic.

Statistical analysis
Age, sex, ulcer size and position, duration of treatment, and H. pylori status were compared between patients with and without hyperplastic
polyps. The $\chi^2$ test was used to compare the two groups in terms of sex, ulcer site (antrum or corpus), ulcer size (with 10 mm as the cutoff point), and $H. pylori$ status. Age, ulcer size, and duration of treatment were compared with Student’s $t$ test. Univariate and multivariate logistic regression analysis were performed to determine factors associated with development of hyperplastic polyps. Significance was accepted at $p<0.05$. Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Polyps characteristics**

Among the 18 patients studied (10 men and 8 women, aged 31–81 years), there were 24 hyperplastic gastric polyps; 20 in the antrum and four in the corpus (Table 1). The second endoscopy at which polyps were discovered was performed at a mean of $3.4 \pm 0.9$ months (2.3–4.3 months) after the first, which was equivalent to the duration of treatment. The mean polyp size was $12.5 \pm 7.8$ mm (4–23 mm). One patient acquired more than one polyp at the site of a single ulcer (Figure 1) and five patients had polyps at the site of multiple ulcers (Figure 2). All polyps were found to be hyperplastic, and none had adenomatous or malignant features.

**Prevalence of $H. pylori$ infection and ulcer size and site**

The age, sex, location of previous ulcers, and treatment duration were similar in patients with and without polyps (Table 2). The overall prevalence of $H. pylori$ infection was slightly higher in the polyp group (77.8%, 14/18) than in the control group (52.9%, 36/68), but the difference were not statistical significant ($p=0.06$). Before treatment, the ulcers were significantly larger in the patients with polyps compared with the control group (14.5 $\pm$ 9.1 mm vs. 6.5 $\pm$ 5.4 mm, $p=0.01$) On stepwise logistic regression, the only factor found to be significantly associated with an increased risk of developing a polyp was having had an ulcer $>10$ mm (odds ratio = 9.03, 95% confidence interval = 2.64–30.91, $p < 0.01$) (Table 3).

**Table 1.** Characteristics of 18 patients with hyperplastic gastric polyps*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td>55.6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.5 $\pm$ 12.8</td>
</tr>
<tr>
<td>Polyp site (n)</td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>20</td>
</tr>
<tr>
<td>Corpus</td>
<td>4</td>
</tr>
<tr>
<td>Size of polyp (mm)</td>
<td>12.5 $\pm$ 7.8 (4–23)</td>
</tr>
<tr>
<td>Single polyps (n)</td>
<td>12</td>
</tr>
<tr>
<td>Multiple polyps (n)</td>
<td>6</td>
</tr>
</tbody>
</table>

*Data presented as n, mean±standard deviation or mean±standard deviation (range).
Endoscopic and histological follow-up of polyps

Of the 18 patients with polyps, eight underwent further endoscopic follow-up after the polyps were discovered. Follow-up endoscopy was carried out after an interval of 3–6 months, for a mean observation period of 17.1 months (range, 5–28 months). Five of the eight patients had *H. pylori* infection at their initial examination, which was successfully eradicated. However, gastric polyps persisted in all eight patients (mean length = 15.4 ± 4.3 mm; range, 8–23 mm). In two patients, the polyps decreased to less than 10% of their initial length, and none of the polyps increased in size. Biopsies were repeated in all eight patients, and the polyps were all hyperplastic, without adenomatous or malignant features.

Table 2. *Helicobacter pylori* status and original ulcer characteristics in patients with and without hyperplastic polyps*

<table>
<thead>
<tr>
<th></th>
<th>Hyperplastic polyp (n = 18)</th>
<th>Control (n = 68)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.5 ± 12.8</td>
<td>53.6 ± 13.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex, male</td>
<td>10 (55.6)</td>
<td>37 (54.4)</td>
<td>0.93</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td>14 (77.8)</td>
<td>36 (52.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ulcer site in antrum</td>
<td>14 (77.8)</td>
<td>42 (61.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ulcer size ≥ 10 mm</td>
<td>14 (77.8)</td>
<td>19 (27.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ulcer size (mm)</td>
<td>14.5 ± 9.1</td>
<td>6.5 ± 5.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Treatment duration (mo)</td>
<td>3.4 ± 0.9</td>
<td>3.3 ± 0.8</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Data presented as n (%) or mean ± standard deviation.

Table 3. Multiple logistic regression analysis of factors related to development of hyperplastic gastric polyps at the site of healed gastric ulcers

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (0.98–1.06)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.05 (0.37–2.98)</td>
<td>0.93</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>3.11 (0.93–10.42)</td>
<td>0.06</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer site in antrum</td>
<td>2.17 (0.64–7.30)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ulcer size ≥ 10 mm</td>
<td>9.03 (2.64–30.91)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment duration (mo)</td>
<td>1.13 (0.56–2.25)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI = confidence interval.

Discussion

The reported incidence of gastric polyps is gradually increasing because of the widespread use of endoscopic examinations. We have described a...
series of patients who acquired hyperplastic gastric polyps in the 3–4 month interval between an initial endoscopic diagnosis of gastric ulcer and a follow-up examination to ensure ulcer healing. Hyperplastic gastric polyps have been reported after electrocoagulation of gastric antral vascular ectasia with Nd:YAG (neodymium-doped yttrium aluminium garnet) laser or argon plasma coagulation.\textsuperscript{14} They have also been noted on the gastric stoma side after Billroth I and II anastomoses.\textsuperscript{15} These stomal polyps might result from the reflux of enteric contents into the remnant stomach. The development of hyperplastic gastric polyps after organ transplantation has been tentatively attributed to altered immune responses associated with immunosuppressive therapy.\textsuperscript{16,17} Our demonstration of hyperplastic polyps growing at the site of healed gastric ulcers could shed further light on the pathophysiology and predisposing factors of such polyps.

Our patients with polyps had larger and deeper ulcers than the control group of patients with healed gastric ulcers but who did not develop polyps. A gastric ulcer > 10 mm was associated with a significantly increased risk of hyperplastic polyps. In fact, this was the only feature on multiple regression analysis that significantly differentiated those with and without polyps. Some authors have hypothesized that the loose connective tissue of the deeper muscularis propria serves as a reservoir for resting fibroblasts or myofibroblasts.\textsuperscript{3} When stimulated by mucosal injury, these cells differentiate, proliferate, and migrate towards the ulcer base. Their function is to synthesize extracellular matrix and participate in mucosal repair. Hyperplastic polyps thus might be the result of over-vigorous regeneration that would be more likely to occur in response to the more severe injury caused by large, deep ulcers that penetrate the deeper muscularis propria.

Of the 18 patients with polyps, eight underwent a third endoscopic follow-up after the polyps were discovered at the second evaluation. Gastric polyps persisted in all eight patients; the polyps decreased to less than 10% of their initial length in two patients; and none of the polyps had grown larger. The most commonly used approach to obtain accurate endoscopic measurements is to introduce an object that closes the lesion and then compare the size of the object and the lesion. Rulers or open biopsy forceps of known size have all been widely used for this purpose. Using an object for reference can minimize the zoom-in and zoom-out effect of imaging that could interfere with the measurement. In addition, there can be substantial variation in size determinations noted between endoscopists. In our study, all the endoscopic evaluations and consecutive measurements were made by the same endoscopist. This could have overcome, at least partially, the subjectivity and poor reproducibility of endoscopic measurements.

Overall \textit{H. pylori} infection was more frequent in patients with polyps (14/18) than in the control group (36/68). Although this difference did not achieve statistical significance, it is possible that the small numbers in our series resulted in a type II statistical error. \textit{H. pylori}-induced damage to the gastric mucosa triggers an inflammatory response with a number of characteristics that might influence ulcer healing. The response includes stimulation of cell proliferation, increased expression of growth factors such as nuclear factor-kB, and inhibition of apoptosis; all factors that might inhibit healing.\textsuperscript{18} The gastrin produced in \textit{H. pylori}-infected antral mucosa might increase cyclooxygenase-2 and prostaglandin production, which is a host response that might actually contribute to ulcer healing.\textsuperscript{19}

A review of randomized controlled trials has suggested that PPIs can heal gastric ulcers in 80–90% of patients at 8 weeks.\textsuperscript{20} However, it has also been suggested that PPIs should be prescribed for longer when the ulcers are large, fibrosed, or unresponsive to treatment.\textsuperscript{21} In our practice, we prescribe PPIs for more than 8 weeks to ensure complete healing of gastric ulcers. In our study, the mean duration of treatment in the polyp and control groups was 3.4 months, and all gastric ulcers in both groups were completely healed.

\textcite{Ji et al} prospectively studied the effect of \textit{H. pylori} eradication on hyperplastic polyps. In the \textit{H. pylori} treatment arm, 15 of 22 patients had
disappearance of the polyps, whereas the polyps persisted in all 21 untreated control patients. In a retrospective study of 43 patients with hyperplastic polyps and *H. pylori* infection, Ohkusa et al found that the polyps disappeared in 33 patients after *H. pylori* eradication but persisted in 10. They stated that the polyps that persisted tended to be larger, but these patients also had persistently higher gastrin levels than those whose polyps disappeared. Despite *H. pylori* eradication in our study, none of the polyps disappeared in the eight patients who were examined for a third time. Why our results differed from the other two studies cited is unclear. In those studies, the polyps were found incidentally and were not associated with ulcers, in contrast to our patients’ polyps that all developed at the site of healed gastric ulcers. Also, the polyps in our study were larger than those investigated by Ji and colleagues (mean = 14.5 mm vs. 6.6 mm).

Abraham et al evaluated the surrounding gastric mucosa of hyperplastic polyps in 160 patients. They found that 85% of the patients had inflammatory mucosal pathology (including active chronic gastritis and atrophic gastritis), and focal intestinal metaplasia was found in 37% of patients. In our study, 10 of 18 patients (56%) had active chronic gastritis and one (5.6%) had focal intestinal metaplasia. These results suggest an association between various forms of gastritis and the development of hyperplastic polyps.

Neither age nor sex differed among our 18 patients with polyps and the 68 without polyps. The demographic characteristics thus cannot account for the varying patterns of gastric ulcer, ulcer healing, and growth of hyperplastic polyps. It could be that part of the answer lies in cytokine gene polymorphisms that result in varying gastric mucosal response to injury and healing.

Nevertheless, our finding that hyperplastic polyps are more likely to be associated with large gastric ulcers and underlines the important role of mucosal injury in the genesis of these polyps. We believe that our study supports the view that hyperplastic polyps could be regenerative lesions that arise at the site of previous severe mucosal injury. We suspect that *H. pylori* infection might play a role because of its association with disordered immune responses, although we were not able to demonstrate conclusively such an association in our small series of patients. Further investigations should focus on the coordinated interaction of all structural layers of the gastric wall during gastric ulcer healing, and mechanisms such as collagen synthesis in the submucosa and muscularis propria, gastrin effects, and expression of growth factors in hyperplastic polyps.

**Acknowledgments**

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**References**