Neoplasms arising in large gastric hyperplastic polyps: endoscopic and pathologic features CME

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Background: Little is known about gastric neoplasms arising from hyperplastic polyps (HPs).

Objective: To investigate the risk factors associated with neoplasms within HPs and to evaluate the role of alterations of the p16-cyclin D1-pRb pathway in the malignant transformation of HPs.

Design: Retrospective, case-control study.

Setting: Tertiary-care center.

Patients: Between May 1995 and January 2011, a total of 809 HPs >1 cm were investigated. Associated neoplasms were present in 30 HPs (case group); 30 HPs without neoplasms were selected as a control group.

Interventions: Gastric polypectomy.

Main Outcome Measurements: The risk factors associated with neoplasms within HPs and immunohistochemical expression of p16, cyclin D1, p53, and Ki-67 between case and control groups.

Results: Of the 809 HPs, 15 had associated dysplasia, and 15 had carcinoma. Multivariate analysis showed that neoplasm was associated with patient age (odds ratio [OR] 1.159; 95% confidence interval [CI], 1.243-2.044; $P < .001$), polyp size (OR 1.103; 95% CI, 1.055-1.152; $P < .001$), and polyp lobulation (OR 4.549; 95% CI, 1.759-11.0766; $P < .001$) but not with location, multiplicity, intestinal metaplasia, growth pattern, or *Helicobacter pylori* infection. Loss of p16 expression and high Ki-67 expression were observed in dysplastic areas of HPs compared with the control group (p16 = 14.3% vs 60%; $P = .001$, Ki-67 = 60.7% vs 36.7%; $P < .001$). However, no significant differences were found in nondysplastic areas in both groups.

Limitations: Single-center, retrospective study.

Conclusion: HPs >1 cm may indicate the presence of neoplasms. Loss of p16 and high Ki-67 expression may be markers of HP-associated dysplasia. (Gastrointest Endosc 2014;80:1005-13.)

Gastric hyperplastic polyps (HP) are among of the most common types of stomach polyps detected during EGD, with a prevalence as high as 60%.[1] Although their specific etiology has not been determined, HPs have been associated with conditions such as autoimmune gastritis and *H pylori* infection.[2] HPs can occur anywhere in the gastric mucosa but are more commonly found in the antrum and are detected as sessile and/or pedunculated

Abbreviations: CDK, cyclin-dependent kinase; HP, hyperplastic polyp.

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polyps during endoscopy. Histologically, these polyps are composed of 2 parts: dilated, elongated, and tortuous foveolae lined by gastric mucin-containing epithelium and edematous stroma infiltrated by mixed inflammatory cells. Focal intestinal metaplasia is also observed.[3]

Although HPs in the stomach are generally considered benign or reactive in nature, there have been reports of associated dysplasia or carcinoma arising within 0.6% to 19% of HPs.[4-7] Risk factors for carcinoma within HP include large size ($\geq$1 cm), pedunculated shape, history of gastrectomy, and a synchronous neoplastic lesion at other sites of the stomach mucosa.[6-9] These previous studies, however, evaluated small numbers of patients, with few direct comparisons of pathology findings in HPs with and without neoplasm.

Little is known about molecular alterations or pathways that may be associated with malignant transformations of HPs. Studies have suggested that p53 is overexpressed, and Ki-67 labeling is high in neoplastic areas of HPs.[9-11] In addition, p21 and cyclin D1 may play important roles in malignant transformation.[12] Similar results have been reported in gastric carcinomas.[13-15] Taken together, these results indicate that alterations in the p16-cyclin D1-pRb pathway, which is central to the regulation of the Gap1-synthesis (G1-S) phase transition in the cell cycle, may be associated with malignant transformation of HPs.

To investigate the risk factors associated with neoplasms within HPs, we compared the endoscopic and clinicopathologic features of gastric HPs that did and did not harbor areas of neoplasia (defined as dysplasia and/or carcinoma). In addition, we evaluated the role of alterations in the p16-cyclin D1-pRb pathway in the malignant transformation of large HPs by comparing the levels of expression of p16, cyclin D1, Ki 67, and p53 between the case and control groups by immunohistochemical staining. Furthermore, we determined whether immunohistochemical staining of forceps biopsy samples could help predict neoplasms in large HPs.

PATIENTS AND METHODS

Selection of patients and evaluation of endoscopic and/or histologic findings

The records of all patients who underwent endoscopic resection in the stomach and were diagnosed as having hyperplastic polyp in a pathology report were retrieved between May 1995 and January 2011 from the archived database of the Asan Medical Center. A total of 998 patients (604 men, 394 women; median age 60 years, interquartile range [IQR] 51-67 years) were identified, with 1027 HPs. Polyps >1 cm in greatest dimension were selected, whereas those with no record of endoscopic findings or no available slides for pathology evaluation were excluded. Finally, 809 HPs in 784 patients (471 men, 313 women; median age 60.5 years, IQR 51-67 years) were analyzed.

Take-home Message

- Endoscopic resection should be considered for hyperplastic polyps >1 cm because endoscopic forceps biopsy may be insufficient to show areas of neoplasm.

Baseline patient characteristics including age, sex, body mass index, alcohol intake, and smoking history were obtained from medical records. This study was approved by the Institutional Review Board of Asan Medical Center.

All endoscopic findings were reviewed by 2 experienced GI endoscopists (K.D.C., J.Y.A.). General characteristics including polyp size, shape, multiplicity, and location were evaluated. Polyp shapes were classified as sessile, semipedunculated, and pedunculated. Polyp lobulation also was evaluated in polyps that were segmented into more than two lobules (Fig. 1). The presence or absence of *H pylori* was assessed by histologic examination of biopsy specimens, a rapid urease test (CLO test; Hp kit, CKD Bio, Korea), or ^{13}C-urea breath tests (Helikit UBT; Isotechnika, Alberta, Canada). *H pylori* status was considered positive if any of these test results were positive.

Endoscopic procedures

Patients were sedated with intravenous midazolam (0.05 mg/kg) and pethidine (50 mg), and their cardiorespiratory functions were continually monitored throughout the procedure. Various endoscopic systems (GIF-XQ230, GIF-XQ240, GIF-Q240, GIF-Q250, GIF-Q260, and GIF-H260; Olympus Optical Co Ltd, Tokyo, Japan) were used over the 16-year period for endoscopic resection. For polypectomy and EMR, after lesion identification, saline solution containing epinephrine (0.01 mg/mL) mixed with indigo carmine was injected into the submucosal layer by using a 21-gauge needle, and the raised lesion was removed by using an SD-9U-1 or SD-12U-1 snare (Olympus), with or without circumferential mucosal incision. For endoscopic submucosal dissection, the typical procedure involved marking, circumferential incision, and submucosal dissection with various knives, such as a needle-knife (MTW Endoskopie Co Ltd, Wesel, Germany) or an insulated-tip knife (Olympus). Endoscopic hemostasis was maintained with hemoclips or hemostatic forceps (FD-410LR; Olympus) whenever bleeding or an exposed vessel was observed.

Nested case-control study and histologic evaluation

After histologic review of all polyps by 2 independent pathologists (D.H.S., Y.S.P.), 30 HPs (3.7%) harboring dysplasia and/or carcinoma were identified (Fig. 2). From the rest of the patients, 30 HPs were randomly selected as the control group and matched by patient age (within 5 years) and polyp size (within 10mm). The control group did not bear areas of dysplasia and/or carcinoma.