Predictable Marker for Regression of Barrett’s Esophagus by Proton Pump Inhibitor Treatment in Korea

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Background/Aims
There has been no report regarding the regression of Barrett’s esophagus (BE) by continuous treatment of proton pump inhibitor (PPI). The aim of this study was to determine the regression rate of BE by PPI and predictable markers related to regression.

Methods
Thirty-five patients diagnosed as BE were consecutively enrolled and most of them took continuous PPI. The 25 patients underwent endoscopic surveillance and received biopsy. If the specialized intestinal metaplasia (SIM) was lost at any point of surveillance and did not recur, the case was regarded as the regression group. The proportion of SIM was graded and the mucin phenotype was decided using immunohistochemistry for MUC2, MUC5AC and MUC6. To assess the cell proliferation indexes and the degree of intestinal maturation, immunohistochemistry for Ki67 and CDX2 were performed.

Results
The regression of BE occurred in the 11 (44%) patients. The clinical and demographic factors showed no difference between the regression (n = 11) and persistence group (n = 14). The lower grade of SIM (P < 0.001) and gastric predominant mucin phenotype (P = 0.018) were more frequent, and the number of Ki67 positive cell per gland (P = 0.008) and the mean extent of CDX2 (P = 0.022) were lower in the regression group than in the persistence group.

Conclusions
The regression of BE by PPI treatment was frequent in Korea. The immunohistochemical detection of mucin phenotype, grade of SIM, Ki67 and CDX2 expression in Barrett’s mucosa could be useful as a predictable marker for regression of SIM in BE.

Key Words
Barrett esophagus; Biologic markers; Regression
Introduction

Although controversies over the definition of Barrett’s esophagus (BE) have continued, BE is commonly diagnosed when there is an endoscopically irregular Z-line and the replacement of the normal stratified squamous epithelium by columnar epithelium with specialized intestinal metaplasia (SIM) containing goblet cells in a biopsy of the distal esophagus. Recently, the prevalence and incidence of BE in Asia has been expected to increase with the availability of gastroscopy and with the increased prevalence of reflux esophagitis related to obesity. Moreover some studies showed that the mean age at the time of diagnosis of BE was getting younger below the age of 50 years. BE is well known as a precancerous lesion. That is, the annual risk of development of esophageal adenocarcinoma from BE was estimated to be approximately 0.5% and 5-year survival rate of esophageal adenocarcinoma was reported as low as below 15%. For this reason, endoscopic surveillance according to grade of dysplasia was considered as indispensable exam to detect complication of BE as early as possible.

The appropriate predictable marker is considered to play an important role in the surveillance of BE patients. However, there has been no clinically established biomarker to predict to the progression or regression of BE so far. In addition, there has been a debate about the degree of SIM, which increases the risk of esophageal adenocarcinoma.

The short-segment BE (SSBE) in Western countries has been reported to be 6 to 12% among all subjects undergoing esophagogastroduodenoscopy (EGD) for screening. However, the prevalence of BE in the nationwide study was reported to be only 0.84% and that of long-segment BE (LSBE) was also very low in the general Korean population. Regarding the reversibility of SSBE, the normalization rate of SIM by continuous treatment of proton pump inhibitors (PPIs) has been reported to reach up to 30% in Western countries, where the prevalence of BE is rather high. In addition, one study from Hong Kong showed that there was a small, but statistically significant regression of BE after the PPI treatment, both in length and in area compared to histamin 2 blocker treatment. However, there has been no report on the regression of BE in Korea. From this background the aim of this study was to determine the regression rate of BE by PPIs and to investigate the predictors that could be useful in determining the regression of BE, including clinical, demographic and histopathologic factors.

Materials and Methods

Patients and Endoscopic Examination

A total of 35 patients (25 male and 10 female) diagnosed as BE by the presence of SIM at initial EGD were consecutively enrolled from April 2005 to June 2012. These patients had an average age of 35 ± 2.2 years (range 32-78). They completed a validated gastroesophageal reflux questionnaire concerning presence or absence of gastroesophageal reflux disease (GERD) symptoms, predominant GERD symptoms, grade and frequency of predominant symptom and use of PPIs. Diagnosis of Helicobacter pylori was performed by histology (by modified Giemsa staining), and Campylobacter-like organism (CLO) test (Delta West, Bentley, Australia), which were tested with the mucosa of antrum and corpus, respectively. The GERD symptoms were prospectively analyzed using GERD impact score. Patients with systemic diseases requiring chronic medication (except hypertension and diabetes mellitus) were excluded (1 patient with a history of gastrointestinal surgery and 1 patient with liver cirrhosis). Finally, 25 patients of remaining 33 patients underwent endoscopic surveillance and received biopsy. All endoscopies were performed and recorded by one experienced endoscopist (N.K.). The distal portion of the esophagus was evaluated carefully to determine the presence of mucosal injury. The presence of endoscopic BE was determined by the identification of the detectable upward displacement of the squamous-columnar junction. The squamous-columnar junction was defined as the location at which the light-pink colored mucosa of the squamous-lined esophagus joined the red columnar-lined esophagus. Esophagogastric junction was defined as the level of the proximal margin of the gastric mucosal folds. In patients with hiatal hernia, this junction was defined by the proximal margin of gastric folds. The length of the BE was defined as the distance between the esophagogastric junction and squamous-columnar junction. Reflux esophagitis was defined according to the Los Angeles classification. Principally the biopsy samples were taken according to a stepwise four-quadrant biopsy procedure with 1-cm interval from just below the squamous-columnar junction. However, 2 biopsy samples were taken from just below the squamous-columnar junction, mainly because all had the SSBE and most of them showed tongue like projection rather than the circumferential finding. If the BE showed no change at surveillance, biopsy specimens were taken at the previous biopsy site re-