Determinants of Intestinal Metaplasia Within the Columnar-Lined Esophagus

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Hypothesis: The clinical and physiological features of patients with short segments of columnar-lined esophagus (CLE) with and without intestinal metaplasia (IM) are distinct.

Design: Retrospective case series.

Setting: University tertiary referral center.

Patients: Sixty-five consecutive patients with a 2-cm or shorter length of endoscopically visible CLE.

Interventions: The type of CLE and the presence of Helicobacter pylori were determined by histopathologic examination of esophageal and gastric antrum biopsy specimens. All patients underwent esophageal manometry and simultaneous 24-hour pH and bilirubin monitoring.

Main Outcome Measures: Clinical and physiological data were compared in patients with and without IM.

Results: Thirty-six patients had IM and 29 had cardiac-type mucosa without IM in biopsy specimens from the CLE. There was no significant difference in age or sex distribution, but the duration of symptoms was significantly longer in patients with IM (10 vs 5 years; P = .03). Abnormal esophageal acid exposure was found in 30 (83%) of 36 patients with IM and 23 (79%) of 29 patients without IM. The prevalence of abnormal bilirubin exposure was significantly higher in patients with IM (75% [27/36]) than in those without IM (41% [12/29]; P = .01). There was no significant difference in the prevalence of H pylori infection between the 2 groups (8% vs 10%; P > .99).

Conclusions: Patients with short segments of CLE and IM have similar esophageal acid exposure but significantly higher frequency of abnormal bilirubin exposure and longer median duration of reflux symptoms than patients without IM. Therefore, CLE, regardless of histological type, is a manifestation of gastroesophageal reflux disease. The presence of duodenoesophageal reflux and the duration of reflux seem to be important in the pathogenesis of IM.

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Before World War II, the finding of columnar epithelium in the tubular esophagus was an uncommon event in clinical practice. Barrett’s classic description was published in 1950, and intestinal metaplasia (IM) occurring within the columnar-lined esophagus (CLE), both of which are now required for the diagnosis of Barrett esophagus, was first recognized in the early 1960s. During the past several decades, the prevalence of Barrett esophagus has dramatically increased, from 1 per 1000 endoscopies in the early 1980s to 10 per 1000 endoscopies in the late 1980s to more than 55 per 1000 endoscopies at present.1 Long-segment (>3 cm) Barrett esophagus is currently identified in 4% to 6% of patients with reflux symptoms, 1% of all upper endoscopies, and 0.3% of the US population. Short-segment (<3 cm) Barrett esophagus is probably equally prevalent, effectively doubling the size of the population at risk.2-4 The presence of IM in a CLE has been linked to a more than 40-fold increased risk of developing esophageal adenocarcinoma, which has also exploded in prevalence over the past 3 decades.5-7

Clinical features associated with Barrett esophagus include long-standing gastroesophageal reflux disease (GERD), a profound loss of the gastroesophageal barrier, and mixed reflux of gastric and duodenal contents into the esophagus. Barrett esophagus is likely the result of damaged squamous epithelium being replaced by cardiac-type mucosa, within which IM can develop.2,8-10 The pathogenesis of IM is incompletely understood. It is unknown why some patients with a CLE.
PATIENTS AND METHODS

PATIENT POPULATION

Between April 1995 and March 1999, 414 consecutive patients were evaluated at the Department of Surgery, University of Southern California School of Medicine, Los Angeles, with endoscopy, esophageal manometry, and simultaneous esophageal pH and bilirubin monitoring because of symptoms suggestive of foregut disease—typical heartburn, regurgitation, dysphagia, noncardiac chest pain, epigastric pain, or symptoms suggestive of aspiration, such as recurrent pneumonia, wheezing, and persistent cough. Patients with a named motility disorder and previous gastric or esophageal surgery were excluded. The study population consisted of 65 patients (42 men and 23 women; median age, 52 years [range, 30-85 years]) in whom an endoscopically evident segment of esophageal columnar lining of 2 cm or less was found. The length of the columnar segment was limited to less than 3 cm because the prevalence of IM in longer segments rises rapidly and is nearly 100% in segments 3 to 4 cm long.11

ENDOSCOPIC IDENTIFICATION OF THE CLE

Three endoscopic measurements were made in all patients. First was the location of the diaphragmatic crura, identified by having the patient sniff. Second was the location of the gastroesophageal junction defined by the proximal extent of the gastric rugal folds where the tubular esophagus begins. A hiatal hernia was diagnosed when the difference between the position of the crural impression and the gastroesophageal junction was 2 cm or more. The third measurement was the squamocolumnar junction, which was identified by the transition from pink-appearing glandular mucosa to white-appearing squamous epithelium. A CLE was suspected when the squamocolumnar junction or any part of its circumference extended above the gastric rugal folds. This included an irregular squamocolumnar junction with tongues of columnar mucosa extending into the esophagus. The presence of a CLE was confirmed on histological evaluation of biopsy specimens. The extent of the columnar-lined segment was defined as the distance from the gastroesophageal junction to the location of the highest point of the squamocolumnar junction. Multiple biopsy specimens were obtained from the columnar-lined segment in all patients. Each biopsy site was recorded, and the presence of erosive esophagitis was noted.

HISTOLOGICAL ASSESSMENT

All biopsy specimens underwent routine fixation and staining with hematoxylin-eosin. Cardiac-type mucosa was characterized by glands composed entirely of mucous cells without any parietal or chief cells. Specialized IM was identified by the presence of well-defined goblet cells within columnar epithelium. The presence of goblet cells was confirmed by Alcian blue staining at pH 2.5.

develop IM within it and others do not. Similarly, the etiology and significance of a CLE without IM, a condition endoscopically identical to short-segment Barrett esophagus, is unclear. Patients with this condition have never been studied, and its relationship to GERD and Helicobacter pylori is unknown. It is possible that patients with segments of pure cardiac mucosa, over time and under the proper luminal conditions, develop IM and its associated risk of progression to dysplasia and adenocarcinoma.

STATIONARY MANOMETRY

Standard stationary motility was performed after an overnight fast. Lower esophageal sphincter resting pressure was measured at the respiratory inversion point as previously described.12 Resting pressure, overall length, and abdominal length were calculated from the mean of 5 recordings. A structurally defective sphincter was defined by a resting pressure of less than 6 mm Hg, overall sphincter length of less than 2 cm, abdominal length of less than 1 cm, or a combination of these.

COMBINED AMBULATORY ESOPHAGEAL pH AND SPECTROMETRIC BILIRUBIN MONITORING

Esophageal bilirubin monitoring was performed simultaneously with pH monitoring. A glass electrode (Ingold Incor, Urdorf, Switzerland) and a fiberoptic probe designed to detect bilirubin (Bilitec 2000; Medtronic Synectics, Shoreview, Minn) were passed transnasally and positioned 5 cm above the upper border of the manometrically defined lower esophageal sphincter. Esophageal pH was recorded on a portable digital data recorder and was analyzed as previously described.13 Patients were instructed to carry out their normal daily activities but to avoid strenuous exertion. A diary was kept of food and fluid intake, symptoms, and time spent in the supine and upright positions. Patients with esophageal pH less than 4 for more than 4.4% of the recorded time were classified as having abnormal esophageal acid exposure.

Esophageal bilirubin exposure was measured by spectrophotometry based on the specific light absorption of bilirubin at a wavelength of 453 nm and recorded on a portable optoelectric data logger.14-16 An absorbance threshold of 0.2 was selected, and bilirubin exposure was quantified as the percentage of time above this threshold.15 The fiberoptic probe was calibrated in water before and after monitoring. Records with a bilirubin absorbance drift of 0.15 or more were discarded. Patients were instructed to follow a special diet, which involved restriction to 3 meals a day and no food with an absorbance similar to that of bilirubin.18 Twenty-four-hour bilirubin absorbance data were analyzed with a software program (Gastrosoft, Irving, Tex) to calculate the total percentage of time bilirubin absorbance was greater than 0.2 during the total monitered period. Based on the study of 35 healthy control subjects, the upper limit of normal for bilirubin exposure was 1.7% of the total time above the absorbance threshold of 0.2.13,15,16

STATISTICAL ANALYSIS

Data are reported as medians and interquartile ranges unless otherwise stated. The Fisher exact test was used to compare proportions between 2 groups and the chi square test was used to compare proportions between more than 2 groups. For continuous data, the Mann-Whitney U test was used to compare 2 groups and the Kruskal-Wallis test was used to compare more than 2 groups.
Factors that affect intestinalization have been difficult to study because in most patients with long segments of cardiac-type mucosa in their esophagus, the process of intestinalization has already occurred.\textsuperscript{11} Conversely, shorter segments of esophageal columnar lining are less likely to be intestinalized and provide a means to compare different clinical and pathophysiological features between patients with and without IM.

The aim of this study was to identify potential risk factors for the development of IM within a CLE by characterizing and comparing physiological, demographic, and clinical data in patients with and without IM in short segments of esophageal columnar lining.

**RESULTS**

Thirty-six patients had IM and 29 had cardiac-type mucosa without IM in biopsy specimens from the CLE. Before the study, acid suppression therapy was given to 32 (89\%) of patients with IM and 26 (90\%) of patients without IM. For one patient in each group there was no available information regarding medical therapy. Table 1 compares the age, sex, and duration of symptoms in patients with short segments of esophageal columnar lining, with and without IM. There was no significant difference the median age or the sex distribution between the 2 groups. The extent of esophageal columnar lining was similar in the 2 groups. Patients with IM had significantly longer duration of foregut symptoms compared with the group with cardiac-type mucosa alone.

Table 2 shows the degree of esophageal exposure to gastric and duodenal juice in patients with and without intestinalized cardiac-type mucosa. There was no significant difference in esophageal acid exposure between the groups. The median percentage of time spent above pH 4 and the prevalence of abnormal bilirubin absorption of 0.2 and the prevalence of abnormal bilirubin exposure, however, were significantly higher in patients with IM.

The prevalence of erosive esophagitis in patients in whom IM was found was not significantly different compared with those without IM (41\% [12/29] vs 50\% [18/36]; \(P = .62\)).

The status of the gastroesophageal barrier and its relation to the presence and absence of IM within a short segment of esophageal columnar lining are shown in Table 3. Lower esophageal sphincter resting pressure, overall length, and abdominal length were similar in both groups. This resulted in a comparable prevalence of mechanically defective sphincters in the 2 groups. There was no significant difference in the prevalence of hiatal hernia.

Esophageal clearance function, including distal esophageal median contraction amplitudes, number of reflux episodes longer than 5 minutes, and duration of the longest reflux episode, were also similar in patients with and without IM within a short segment of esophageal columnar lining (Table 4).


Helicobacter pylori was not found in any of the biopsy specimens of the CLE but was seen in biopsy specimens of the gastric antrum in 3 (8%) of the 36 patients with IM, which was not significantly different from that of patients without IM (10% [3/29]) (P > .99).

**COMMENT**

Short segments of esophageal columnar lining are diagnosed with increasing frequency in the distal esophagus. Only a portion of these patients, however, harbor IM on histologic examination of biopsy specimens. In this study, IM was found in 55% of patients with segments of esophageal columnar lining measuring 2 cm or less. This is similar to studies of other investigators who found IM in 48% to 61% of patients with segments of esophageal columnar lining, with increasing frequency in the distal esophagus. Only a few patients without IM (10% [3/29]) had esophageal columnar lining on histologic examination of biopsy specimens of the CLE but was seen in biopsy specimens of the gastric antrum in 3 (8%) of the 36 patients with IM, which was not significantly different from that of patients without IM (10% [3/29]) (P > .99).

IM develops with age alone. It has been shown that Barrett esophagus is likely the result of injured squamous epithelium being replaced by cardiac-type mucosa within which, over time and persistent inflammation, IM develops. Although the pathogenesis of IM is incompletely understood, it has been suggested that IM develops with increasing age. However, the process of metaplasia is believed to be a consequence of chronic inflammation, and it is therefore unlikely that IM develops with age alone. It has been shown that patients with Barrett esophagus have not only abnormalities in esophageal acid exposure but also a high prevalence of increased esophageal exposure to duodenal juice. This is the first study of esophageal acid and bilirubin exposure in patients with and without IM in a segment of esophageal columnar lining. Abnormal esophageal bilirubin exposure was one of two determinants significantly associated with the presence of IM. This finding further supports the hypothesis that duodenogastroesophageal reflux is important in the pathogenesis of IM.

Not all patients with abnormal esophageal bilirubin exposure had IM. Forty-one percent of patients with a CLE without IM had abnormal esophageal bilirubin exposure, which suggests that other factors might play a role in the development of IM. Possibilities include the underlying genetics of the patient, other components of the reflux not measured by acid or bilirubin testing, or sampling error. It is also possible that some of these patients will develop IM with time if reflux is allowed to continue. Conversely, esophageal bilirubin exposure was normal in 25% (9/36) of the patients with IM, which suggests that abnormal esophageal bilirubin exposure is not essential for the development of IM, although the limitations of ambulatory esophageal bilirubin measurement temper this conclusion. Some of these patients might have false-negative study results; others might be negative because esophageal acid and bilirubin exposure are customarily measured 5 cm above the upper border of the sphincter. This is well above the area of metaplastic change, creating the possibility that abnormal exposure at or within the sphincter, and the area of metaplastic epithelium, exists, despite the normal results 5 cm above.

The second determining factor was the duration of reflux symptoms, which was significantly longer in patients with IM compared with those in whom only cardiac-type mucosa was found. Taken together, these observations suggest that Barrett esophagus is likely the result of injured squamous epithelium being replaced by cardiac-type mucosa, within which, given time and the proper luminal conditions, IM develops as a second step in its pathogenesis.

It is possible that the effect of duodenoesophageal reflux is to modulate the pH of the gastric juice refluxed into the esophagus. Exposure of tissue cultures of Barrett mucosa to pulses of pH greater than 3.5 results in increased villin expression and morphologic evidence of villi formation, both of which suggest the process of intestinalization.

Understanding the risk factors for the development of IM and its associated risk of esophageal adenocarcinoma has significant implications for the management of patients with GERD. Early identification of patients at risk, followed by effective treatment to eliminate the underlying factors associated with the development of IM, may allow interruption of the metaplasia-dysplasia-cancer sequence. Present treatment options include acid suppression therapy and antireflux surgery; both have benefits and risks, although antireflux surgery might be the better alternative. Acid suppression therapy decreases pathologic acid reflux, but reflux of duodenal juice, although reduced, exceeds the normal range in many patients. Furthermore, recent data show that using symptom relief as the end point of therapy is unreliable. Katzka and Castell, Ouatu-Lascar and Tradalifopoulos, and others have shown that 40% to 80% of patients with Barrett esophagus continue to have abnormal esophageal acid exposure despite receiving high doses (20 mg twice daily) of proton pump inhibitors. Antireflux surgery results in more reproducible and reliable elimination of reflux of acid and duodenal content but might be more difficult to maintain in the long term in patients with Barrett esophagus vs those without.

Because the risk of progression to dysplasia and cancer in patients with metaplastic columnar lining of the esophagus depends on the presence of IM, only patients with both features are presently enrolled in surveillance programs.

The magnitude of the risk of developing dysplasia and adenocarcinoma in short-segment Barrett esophagus is unclear. The risk is believed to be less than that in traditional Barrett esophagus because the length of the columnar-lined segment has been shown to be a significant risk factor in the neoplastic progression. Sharma et al prospectively followed up a cohort of 59 patients with short-segment Barrett esophagus for an average of 36.9 months. Five patients had low-grade dysplasia at the time of initial endoscopy and 3 additional patients developed low-grade and 2 developed high-grade dysplasia during follow-up. One patient with high-grade dysplasia subsequently developed adenocarcinoma. The prevalence of dysplasia was 8.5%, and the dysplasia incidence was 5.7% annually. The authors emphasized the need for surveillance of patients with short-segment Barrett esophagus. Further studies are needed to confirm the risk of neoplastic progression in short-segment Barrett esophagus.

The results of the present study suggest that short segments of esophageal columnar lining, with or without IM, are a manifestation of GERD. This is suggested by similar alterations in each group of the hallmarks of GERD, in-
cluding decreased lower esophageal sphincter pressure and length and increased degree of esophageal acid exposure. The prevalence of abnormal esophageal acid exposure, mechanistically defective sphincters, and erosive esophagitis was comparable in the 2 groups. Whether patients with short segments of pure cardiac-type mucosa will subsequently develop IM and whether they should be maintained in endoscopic surveillance programs remains unknown.

Based on the results of this study we conclude that patients with short segments of CLE with IM have similar esophageal acid exposure but significantly higher frequency of abnormal bilirubin exposure and longer median duration of reflux symptoms than patients without IM. These findings suggest that esophageal columnar lining, regardless of histological type, is a manifestation of GERD.

The presence of duodenoesophageal reflux and the duration of reflux may be important in the pathogenesis of IM.

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REFERENCES


DISCUSSION

Lawrence W. Way, MD, San Francisco, Calif: Drs Öberg, Peters, and DeMeester have made another important contribution to knowledge of the pathogenesis of Barrett metaplasia. Their experiment compared the clinical and laboratory findings in 65 patients with 3 cm or less of columnar-lined esophagus (CLE) at the gastroesophageal junction, of whom slightly more than half had intestinal metaplasia, a hallmark of Barrett disease that is almost universally present in long-segment CLE. The results showed a similar severity of acid reflux in those with and without intestinal metaplasia but a longer history of reflux symptoms and a substantially greater exposure of the gastroesophageal junction to reflux of duodenal juice as measured by the bilirubin probe. The implications are that reflux of duodenal juice is an etiologic factor in the pathogenesis of Barrett disease. Their data strongly support the conclusion.

I have 2 questions regarding the patients and their reflux disease. First, although the patients had experienced heartburn for 5 to 10 years and were presumed to have GERD, only 80% of each group was found by pH monitoring to have abnormal acid exposure. Given their long history of symptoms, which included heartburn, and the knowledge that acid reflux is usually quantitatively greater in patients with Barrett disease than in those with less advanced GERD, this is less than expected and raises a

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question about the diagnosis of reflux. What were the absolute reflux scores? They were not reported in the manuscript. What was the treatment history? Were the patients all taking PPI [proton pump inhibitors]? Can you resolve this contradiction?

Finally, were the patients followed by periodic endoscopy, and, if so, how did the disease evolve with time? The study lasted long enough that data should be available to answer this question.

Marco G. Patti, MD, San Francisco: Even though I agree with the final conclusions, it seems to me that 6 patients in each group had normal esophageal acid exposure and 10 patients in each group had normal bilirubin exposure. Why do you think these patients developed columnar-lined epithelium? Why do you think these patients had reflux disease?

Dr Peters: The clinical significance of this is 2-fold. One, although there remains significant controversy regarding the treatment of Barrett esophagus, the real holy grail of this premalignant lesion, like with any premalignant lesion, is its prevention. As we see more of this disease, we need to start thinking about preventing it. In order to do that, we need to identify the risk factors that create it. Second, there is considerable discussion about exactly when, in patients with reflux disease, we should intervene with an endoscope. This study provides us with a little bit of information in that regard, as have other epidemiologic studies. It is beginning to emerge that if you have symptoms for more than 3 or 6 years, someone should drop an endoscope down to make sure that you do not have intestinalization of your esophagus.

With that background, let me answer the questions. Both Dr Patti and Dr Way asked why some of the population have negative pH studies and Biatte studies, given that we are studying GERD. This is asked on a background of years of equating a positive pH study with the presence of reflux disease. Recently, really with the introduction of the laparoscope, surgeons started to see earlier and earlier disease and thus started to study early disease. This study focuses on a population of patients, by the selection criteria, that has early disease, ie, very small changes at the gastroesophageal junction. Remember, a pH probe is placed 5 cm above the upper border of the lower esophageal sphincter. The sphincter is about 4 cm long and probably straddles the gastroesophageal junction. So, the pH probe and the Biatte probe are placed well into the lumen of the esophageal body and well above the gastroesophageal junction.

What we learned as we began to study the epithelial changes at the gastroesophageal junction is that the epithelium is probably a better indicator of the presence of reflux disease than the pH probe or was. One immediately runs into a conceptual problem in studying these patients, ie, how to define the disease. As we search for new markers, old standards may be inadequate. We are left with identifying the hallmarks of disease and selecting patients who we think have these for study. It is true that about 10% to 20% of these patients do not have positive pH studies if you look 5 cm above the gastroesophageal junction. We, and other investigators, are beginning to place the pH probe lower in order to understand a little bit more about normality and abnormality at the gastroesophageal cardia. This is relevant to the incidence of Barrett of the cardia and cardia adenocarcinoma. These arguments also get to the question about the composite scores and the percentage of patients on PPI treatment and the percentage of patients that are symptomatic. None of those correlate terribly well with the presence or absence of early disease.

The question that Dr Way asked about periodic endoscopy is an important one. The world presently believes that we cannot alter the natural history of Barrett esophagus. As we study this disease earlier and earlier, we are beginning to realize that maybe that conclusion is not quite as set in stone as we thought it was. All the patients with intestinalization of these short segments do get periodic endoscopy. In the absence of intestinalization, because there is no malignant risk, they do not. We have recently reported in a paper that Steve DeMeester presented last year at the American Surgical Association that maybe we can reverse or lose the intestinalization in patients with short-segment Barrett esophagus. Others have now confirmed that fact. The group at the University of Washington, which has a very different bias than we do, have reported similar findings. This is an evolving science. We are beginning to understand a little bit about the early aspects of gastroesophageal reflux disease and maybe some of the risk factors that predispose to Barrett esophagus.

ARCHIVES OF INTERNAL MEDICINE

Tea Flavonoids May Protect Against Atherosclerosis: The Rotterdam Study

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Background: Epidemiological studies have indicated a protective role of dietary flavonoids in cardiovascular disease, but evidence is still conflicting. Tea is the major dietary source for flavonoids in Western populations. We studied the association of tea intake with aortic atherosclerosis in a general population.

Methods: The present analysis formed part of the Rotterdam Study, a prospective study of men and women 55 years and older. Dietary intakes were assessed at baseline by a trained dietician who used a semiquantitative food frequency questionnaire. Calcified plaques in the abdominal aorta were radiographically detected after 2 to 3 years of follow-up. Aortic atherosclerosis was classified as “mild,” “moderate,” or “severe,” according to the length of the calcified area (<1 cm, 1-5 cm, and >5 cm, respectively). The association of tea intake with severity of aortic atherosclerosis was studied in 3454 subjects who were free of cardiovascular disease at baseline. Data were analyzed by logistic regression, adjusting for age, sex, body mass index (calculated as weight in kilograms divided by the square of height in meters), smoking, education, and intake of alcohol, coffee, vitamin antioxidants, total fat, and total energy.

Results: Multivariable analyses showed a significant, inverse association of tea intake with severe aortic atherosclerosis. Odds ratios decreased from 0.54 (95% confidence interval [CI], 0.32-0.92) for drinking 125 to 250 mL (1-2 cups) of tea to 0.31 (CI, 0.16-0.59) for drinking more than 500 mL/d (4 cups per day). The associations were stronger in women than in men. The association of tea intake with mild and moderate atherosclerosis was not statistically significant.

Conclusion: This study indicates a protective effect of tea drinking against ischemic heart disease. (1999;159:2170-2174)

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