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BRIEF ARTICLE

Short-segment Barrett's esophagus and cardia intestinal metaplasia: A comparative analysis

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Abstract

AIM: To investigate the endoscopy and histology of short-segment Barrett's esophagus (SSBE) and cardia intestinal metaplasia (CIM), and their correlation with *Helicobacter pylori* (*H. pylori*) gastritis and gastroesophageal reflux disease (GERD).

METHODS: Biopsy specimens were taken from 32 SSBE patients and 41 CIM patients with normal appearance of the esophagogastric junction. Eight biopsy specimens from the lower esophagus, cardia, and gastric antrum were stained with hematoxylin/eosin, Alcian blue/periodic acid-Schiff, Alcian blue/high iron diamine and Gimenez dye. Results were graded independently by one pathologist.

RESULTS: The SSBE patients were younger than the CIM patients ($P < 0.01$). The incidence of dysplasia and incomplete intestinal metaplasia subtype was higher in SSBE patients than in CIM patients ($P < 0.01$). *H. pylori* infection was correlated with antral intestinal metaplasia ($P < 0.05$), but not with reflux symptomatic, endoscopic, or histological markers of GERD in CIM patients. SSBE was correlated with reflux symptomatic and endoscopic esophagitis ($P < 0.01$), but not with *H. pylori* infection and antral intestinal metaplasia.

CONCLUSION: Dysplasia risk is significantly greater in SSBE patients than in CIM patients. CIM is a manifestation of *H. pylori*-associated and multifocal atrophic gastritis, whereas SSBE may result from GERD.

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Key words: Endoscopy; Barrett's esophagus; Cardia intestinal metaplasia; Esophagogastric junction; Gastroesophageal reflux disease

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INTRODUCTION

The incidence of adenocarcinoma in esophagus and gastroesophageal junction (GEJ) has increased in recent years in North America, Europe, Japan and China[1-3]. Barrett's esophagus (BE) is thought to be a premalignant condition of esophageal adenocarcinoma, accounting for most cases of adenocarcinoma of the GEJ. The reported prevalence of Barrett's-associated adenocarcinoma varies widely, with an average of 10%[4-7]. A meta-analysis[8] of 4120 patients in China reported that BE is found in 2.44% of patients undergoing endoscopy for various symptoms of upper gastrointestinal tract diseases.

It was reported that the frequency of short-segment Barrett's esophagus (SSBE), < 3 cm in length, is increased and implicated as a risk factor for adenocarcinoma of the cardia[9-11]. Endoscopic diagnosis of this entity is difficult and always requires histological demonstration of specialized columnar epithelium (SCE). Since most endoscopists do not perform biopsies unless the columnar epithelium is seen to extend from the proximity to the GEJ. Short segments are frequently unrecognized. Spechler *et al*[12] have recently described the presence of intestinal metaplasia in certain normal-appearing GEJ. The relation of this condition to SSBE has not yet been investigated.

In this study, SSBE and cardia intestinal metaplasia (CIM) were compared and their correlation with *Helicobacter pylori* (*H. pylori*) gastritis and gastroesophageal reflux disease (GERD) was studied, which may contribute to the clinical diagnosis, treatment, prevention, and susceptibility forecast of BE.

MATERIALS AND METHODS

Patients

Tissue specimens used in this study were provided by The Sixth Hospital of Shanghai Jiaotong University, with the approval of the hospital and patients. Endoscopy was performed in a standardized manner by experienced endoscopists. Appearance of the squamocolumnar junction was carefully studied in a prograde view after insufflation of air and retroversion in the stomach. Thirty-two consecutive patients with endoscopically apparent SSBE (< 3 cm in length) included in the study (group A) were selected from The Outpatient Clinic of our hospital over a two-year period. Two endoscopic features of the squamocolumnar transition were considered indicative of SSBE: a straight and regular Z line (< 3 cm) displaced upwards in relation to the GEJ (circumferential type), and an irregular Z line with eccentric tongues of red mucosa extending above the GEJ (digital type). The severity of SSBE was measured according to the Prague C&M classification[13]. The specimens were stained with Alcian blue (pH 2.5).

Group B was consisted of 41 adult ambulatory consecutive patients who underwent upper endoscopy in our endoscopy unit and were considered by the endoscopist to have a normal-appearing GEJ. Patients with a history of cancer or prior gastric/esophageal surgery were excluded, as were those who were unable to give their informed consent, or who had any contraindication to endoscopic biopsies. CIM was defined based on the presence of barrel-shaped goblet cells in normal-appearing GEJ.

All patients included in this study were questioned about symptoms of GERD (heartburn, regurgitation, and odynophagia). Endoscopic signs of esophagitis were recorded and graded according to the Los Angeles classification[14].

Endoscopy and biopsy protocol

Biopsy specimens were taken from 32 patients with SSBE and 41 CIM patients with normal-appearing GEJ. Eight biopsy specimens, taken from the lower esophagus, cardia, and gastric antrum, were stained with hematoxylin/eosin, Alcian blue/periodic acid-Schiff (AB/PAS, pH 2.5), AB/high iron diamine (AB/HID) and Gimenez dye. Results were graded independently by one pathologist.

Table 1 Incidence of dysplasia in short-segment Barrett's esophagus and cardia intestinal metaplasia patients

Patients	*n*	Dysplasia	%
CIM	41	1	2.4
SSBE	32	4	12.5[b]

[b]P < 0.01 *vs* cardia intestinal metaplasia (CIM). Biopsy specimens taken from 41 CIM patients and 32 short-segment Barrett's esophagus (SSBE) patients were stained with hematoxylin and eosin. The incidence of dysplasia was calculated. The incidence of dysplasia was significantly higher in SSBE patients than in CIM patients (12.5% *vs* 2.4%, P < 0.01).

Histology

Formalin-fixed, paraffin-embedded biopsy samples were stained with hematoxylin/eosin. PAS/AB (pH 2.5) was used to show the presence of acid mucins. BE was diagnosed based on the presence of SCE, which was defined by the unequivocal demonstration of intestinal-type goblet cells.

Statistical analysis

Statistical analysis was performed using the χ^2 test.

RESULTS

Incidence of dysplasia in SSBE and CIM patients

The SSBE patients were younger than the CIM patients (P < 0.01). The incidence of dysplasia was higher in SSBE patients than in CIM patients (P < 0.01) (Table 1).

Incidence of incomplete intestinal metaplasia in SSBE and CIM patients

The incidence of incomplete intestinal metaplasia (IM) was significantly different between the two types of epithelium (P <0.01 *vs* CIM) (Table 2).

Prevalence of GERD in SSBE and CIM patients

The prevalence of GERD symptoms was higher in SSBE patients than in CIM patients (P < 0.01), as was endoscopic and histological evidence of esophagitis (Table 3).

Correlation between H. pylori and antral IM in SSBE and CIM patients

The correlation between *H. pylori* infection and antral IM in SSBE and CIM patients is shown in Table 4.

DISCUSSION

Over the past two decades, the incidence of adenocarcinoma of the esophagus and gastric cardia has increased rapidly. BE is recognized as a precancerous lesion of esophageal adenocarcinoma in most cases of adenocarcinoma

Table 2 Incidence of incomplete intestinal metaplasia in short-segment Barrett's esophagus and cardia intestinal metaplasia patients

Patients	*n*	Incomplete IM	Complete IM	%
CIM	41	8	33	19.5
SSBE	32	21	11	65.6[b]
Total	73	29	44	39.7

[b]P < 0.01 *vs* cardia intestinal metaplasia (CIM). Eight biopsy specimens taken from the lower esophagus and cardia were stained with hematoxylin/eosin, Alcian blue/periodic acid-Schiff (pH 2.5), AB/high iron diamine or Gimenez dyes. The prevalence of incomplete intestinal metaplasia (IM) was significantly higher in short-segment Barrett's esophagus (SSBE) patients than in CIM patients (65.6% *vs* 19.5%, P < 0.01).

Table 3 Incidence of reflux symptomatic, endoscopic, or histological markers of gastroesophageal reflux disease in short-segment Barrett's esophagus and cardia intestinal metaplasia patients *n* (%)

Patients	*n*	Reflux symptoms	Endoscopic esophagitis	Histological features of reflux esophagitis
CIM	41	12 (29.3)	5 (12.2)	12 (29.3)
SSBE	32	26 (81.2)[b]	30 (93.8)[b]	31 (96.9)[b]

[b]P < 0.01 *vs* cardia intestinal metaplasia (CIM). All patients were questioned about symptoms of gastroesophageal reflux disease (GERD). Endoscopic signs of esophagitis were recorded and graded. All biopsy specimens were stained with hematoxylin and eosin. Alcian blue/periodic acid-Schiff (pH 2.5) was used to show the presence of acid mucins. The incidence of reflux symptomatic, endoscopic, or histological markers of GERD was higher in short-segment Barrett's esophagus (SSBE) patients than in CIM patients (P < 0.01).

of the GEJ. Progression from metaplasia to dysplasia and adenocarcinoma is well documented[7]. Traditionally, BE is arbitrarily defined as a circumferential segment of columnar-lined epithelium (2 or 3 cm in length) in the lower esophagus. However, this macroscopic definition has been recently questioned, because it excludes shorter segments and "tongues of columnar-lined epithelium", which are frequently found in the distal esophagus, and endoscopic measurements can be imprecise. It has therefore been proposed that the diagnosis of BE should be reserved for patients with IM detected in biopsy specimens from the distal esophagus[15,16]. Recently, the presence of CIM in certain normal-appearing GEJ has been described[17-19]. Detection of IM in the distal esophagus as well as within the gastric cardia has been reported with an increasing frequency[15,16]. It was reported that the prevalence of BE and CIM is 2%-12% and 5%-23%, respectively, in patients undergoing routine upper gastrointestinal endoscopy[20,21]. Detection of IM in BE patients potentially commits the patients to regular surveillance endoscopy with biopsy. The incidence of adenocarcinoma in patients with BE is estimated to be 30-50 times greater than that in general populations, and is on the increase[6,7]. However, the exact incidence of cancer in patients with BE is unknown, and the role of CIM as a premalignant lesion is still unclear. The relation of this condition to BE has not yet been investigated. Whether CIM and IM originating from the esophageal mucosa have a common pathogenesis and

Table 4 Relation between *Helicobacter pylori* infection and antral intestinal metaplasia in short-segment Barrett's esophagus and cardia intestinal metaplasia patients *n* (%)

Patients	*n*	Cardia *H. pylori* infection	Antral IM	Antral *H. pylori* infection
CIM	41	18 (43.9)	21 (51.2)	20 (48.8)
SSBE	32	5 (15.6)[a]	4 (12.5)[b]	7 (21.9)[a]

[a]P < 0.05, [b]P < 0.01 *vs* cardia intestinal metaplasia (CIM). Eight biopsy specimens taken from the lower esophagus, cardia, and gastric antrum were stained with Alcian blue/periodic acid-Schiff (pH 2.5) and Gimenez dyes, respectively. The incidence of *Helicobacter pylori* (*H. pylori*) infection and antral intestinal metaplasia (IM) was lower in short-segment Barrett's esophagus (SSBE) patients than in CIM patients ([a]P < 0.05, [b]P < 0.01).

identically associated risk factors remains unknown.

In the present study, the dysplasia risk was significantly higher in SSBE patients than in CIM patients (12.5% *vs* 2.4%). Sharma *et al*[15] also compared the incidence of dysplasia in 177 SSBE patients and 76 CIM patients. As in our study, the risk of dysplasia differed significantly between the two groups. Dysplasia was detected in 11.3% (20/177) of SSBE patients and in 1.3% (1/76) of CIM patients, indicating that dysplasia is two potentially different clinical processes. Future studies should separate SSBE from CIM to improve our understanding of the pathophysiology and malignant potential of each entity.

Although a few authors reported that the areas adjacent to CIM show normal foveolar epithelium, whereas those adjacent to BE contain pre-goblet cells that can be positively stained with Alcian blue[15,16]. Since these characteristics cannot be found in all biopsy specimens, it is not reliable to distinguish SSBE from CIM histologically. HID/AB staining has also been used to distinguish SSBE from CIM[17-19]. It was reported that IM at the GEJ (or ultra-short-segment BE) is more frequently found to express sulfomucins, which is defined as type Ⅲ IM and involves the surface glandular epithelium[11,17]. Liu *et al*[10] also found that the area covered by incomplete IM is significantly greater and the level of sulfomucins is obviously higher in the esophagus than in the stomach. In our study, the prevalence of type Ⅲ IM was significantly higher in SSBE patients than in CIM patients (65.6% *vs* 19.5%, P < 0.01). HID/AB staining can be used to distinguish SSBE from CIM initially, based on the different expressions of neutral mucins, sialomucins, and sulfomucins.

The incidence of reflux symptomatic, endoscopic, or histological markers of GERD was higher while that of *H. pylori* infection and antral IM was lower in SSBE patients than in CIM patients (P < 0.05). Since CIM is a manifestation of *H. pylori*-associated and multifocal atrophic gastritis, and SSBE can result from GERD, it is necessary to explore new and efficacious diagnostic methods to distinguish BE from CIM.

cDNA microarray methods have been used in the study of gene expression, DNA sequencing, novel genes and mutations, DNA polymorphism, drug screening, diagnosis of disease, and gene mapping, since they were reported by Schena *et al*[22] in 1995. We have previously performed an analysis of three 4096 chips to investigate the difference in gene expression profiles between BE and CIM epithelium[23]. A total of 141 genes were screened that exhibited a differential expression in the three chips. A comparison between the two gene profiles showed that the gene expression patterns were different in BE and CIM epithelium, illustrating that detection of differences in gene expression between BE and CIM with gene chips is a new method for the diagnosis, treatment and prevention of BE. Future studies should separate SSBE from CIM to improve our understanding of the pathophysiology and malignant potential of such diseases.

COMMENTS

Background

The incidence of adenocarcinoma in the esophagus and gastroesophageal junction (GEJ) has increased in recent years. Barrett's esophagus (BE) is thought to be a premalignant condition. Recently, the presence of cardia intestinal metaplasia (CIM) in certain normal-appearing GEJ has been described. The relation between CIM and BE has not yet been investigated.

Research frontiers

Short-segment Barrett's esophagus (SSBE), < 3 cm in length, has been reported as a risk factor for adenocarcinoma of the cardia. Whether CIM and IM originating from the esophageal mucosa have a common pathogenesis still remains unknown. In this study, the authors demonstrated that CIM was a manifestation of *Helicobacter pylori* (*H. pylori*)-associated and multifocal atrophic gastritis, whereas SSBE could result from gastroesophageal reflux disease (GERD).

Applications

This study describing the he different characteristics of SSBE and CIM may contribute to the clinical diagnosis, treatment, prevention, and susceptibility forecast of BE.

Terminology

BE is thought to be a premalignant condition of esophageal adenocarcinoma, accounting for most cases of adenocarcinoma of the GEJ. BE is defined as IM detected in biopsy specimens from the distal esophagus. The extent of the Barrett segment is measured according to the Prague C&M classification.

Peer review

The authors examined the different characteristics of SSBE and CIM and revealed that CIM was a manifestation of *H. pylori*-associated and multifocal atrophic gastritis, whereas SSBE could result from GERD. The results are interesting and may contribute to the clinical diagnosis, treatment, prevention, and susceptibility forecast of BE.

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