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The association of short segment Barrett's esophagus with intestinal metaplasia in stomach

Kısa segment barrett özofagusun midedeki intestinal metaplazi ile ilişkisi

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Background/aims: *The aims of this study were to investigate the presence of short segment Barrett's esophagus in people found to have tongue-like columnar mucosal protrusions in the distal esophagus and to determine the relationship between short segment Barrert's esophagus and Helicobacter pylori, gastritis and intestinal metaplasia observed in other parts of the stomach.* ***Methods:*** *The study included 50 patients (32 male, 18 female). Two biopsy specimens were taken from the antrum, at least 2 cm away from the pylorus, from the incisura angularis, corpus and cardia and four biopsy specimens were taken from tongue-like columnar protrusions (<3 cm long) above the gastroesophageal junction. Tissue samples were stained with hematoxyline-eosine, HID-Alcian blue pH 2.5 and modified Giemsa.* ***Results:*** *Of the 50 subjects who were found to have tongue-like columnar protrusions above the gastroesophageal junction, short segment Barrett's esophagus was detected in nine (18%). Whereas all short segment Barretti's esophagus cases were associated with chronic gastritis, Helicobacter pylori was found to be positive in five (55.5 %) of them and there was intestinal metaplasia in other parts of the stomach (antrum in two patients, incisura angularis in three, antrum and cardia in one) in six (66.6 %) cases. In 41 patients without short segment Barrett's esophagus 33 (80%) had chronic gastritis, 27 (66%) had Helicobacter pylori infection and eight had intestinal metaplasia in different locations (there in antrum, four in incisura angularis, one in the antrum and cardia) of the stomach.* ***Conclusions:*** *An association between short segment Barrett's esophagus and intestinal metaplasia was found in different parts of the stomach. The link between intestinal metaplasia in the stomach and these metaplastic changes in the tubular esophagus requires evalation in larger and more comprehensive studies.*

Key words: : Short segment Barrett's esophagus, Intestinal metaplasia, *Helicobacter pylori,* Chronic gastritis.

Amaç: *Distal özofagusta dil şeklinde kolumnar mukozal uzantıları olan hastalarda kısa segment Barrett özofagus (KSBO) varlığını araştırmak ve kısa segment Barrett özofagus ile H.pylori, kronik gastrit ve midenin farklı lokalızasyonlarında saptanan intestinal metaplazi arasındaki ilişkiyi belirlemektir.* ***Yöntem:*** *Distal özofagusta dil şeklinde kolumnar mukozal uzantıları (< 3cm uzunlukta) saptanan 50 hasta (32 erkek, 18 kadın) çalışmaya alındı. Biyopsiler sırasıyla antrum, incisura angularis, korpus büyük kurvatur ve kardiadan iki adet, gastroözofageal bileşkenin üzerindeki mukozal uzantılardan dört adet olmak üzere alındı. Doku örnekleri hematoxyline-eosine, HID-Alcian blue pH 2.5 ve modified Giemsa ile bayandı.* ***Bulgular:*** *gastroözofageal'nin üstünde dil şeklinde kolumnar mukozal uzantıları olan 50 hastanın dokuzunda (%18) kısa segment Batters özafagus tespit edildi. Kısa segment Barrett özofagus saptanan olguların tümünde kronik gastrit, beşinde (%55) H.pylori pozitifliği, altısında (%66) midenin farklı lokalızasyonlarında (antrum 2, incisura angularis 3, antrum ve kardia 1) intestinal metaplazi bulundu. Oysa kısa segment Barrett özofagus saptanmayan 41 olgunun 33'ünde (%80) kronik gastrit, 27'sinde (%66) H.pylori, sekizinde (%19.6) midenin farklı lokalızasyonlarında (antrum 3, incisura angularis 4, antrum ve kardia 1) intestinal metaplazi tespit edildi.* ***Sonuç:*** *Kısa segment Barrett özofagus, midenin farklı lokalızasyonlarında tespit edilen intestinal metaplazi ile birliktelik gösteriyordu. Şöyle ki kısa segment Barrett özofagus'lu olguların 2'sinde antrum, 3'ünde insisura angularis, birinde antrum ve kardiyada metaplazi tespit edilirken, kısa segment Barrett özofagus saptanmayan olguların 3'ünde antrum, 4'ünde insisura angularis ve birinde korpusta metaplazi saptandı. Tubuler özofagus içinde saptanan bu metaplazik değişiklikler ile midedeki intestinal metablaplazinin birlikteliğine dair daha kapsamlı çalışmaların yapılması yararlı olacaktır.*

Anahtar kelimeler: Kısa segment Barrett özofagus. Intestinal metaplazi, *Helicobacter pylori,* Kronik gastrit

INTRODUCTION

Barrett's esophagus (BE) is an acquired condition in which columnar epithelium containing goblet cells replaces the squamous epithelium that normally lines the distal esophagus (1,2). It is considered to be a premalignant condition, with gastroesophageal reflux disease (GERD) playing a major role in its development (3-5). Although the epidemiology of BE has not been fully described, the relationship between Barrett's epithelium and esophageal adenocarcinoma has been illustrated in numerous studies (1,4,6,7). Barrett's esophagus can be classified into three groups: long segment

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Barrett's esophagus (LSBE), short segment Barrett's esophagus (SSBE) and junctional intestinal metaplasia (ultra-short segment Barrett's) (5-6).

Short segment Barrett's esophagus is defined by the presence of columnar-appearing mucosa (<3 cm in length) with intestinal metaplasia (IM) in the distal esophagus on biopsy (6-10).

In patients with GERD, SSBE is more common than LSBE. Although the latter has a typical endoscopic appearance, SSBE can not be diagnosed easily by endoscopy (4).

The epidemiological characteristics of SSBE are different from IM detected at the gastroesophageal junction (GEJ). Thus, IM occurring within columnar-appearing mucosal protrusions should be differentiated from that which occurs just beneath a normal appearing squamocolumnar junction (SCJ or Z-line) (6).

The aim, of this study'were to investigate the presence of intestinal metaplasia, tongue-like columnar mucosal protrusions (< 3cm long) above the GEJ and to evaluate the relationship between SSBE and *Helicobacter pylori (H.pylori),* chronic gastritis and IM seen in other regions of the stomach.

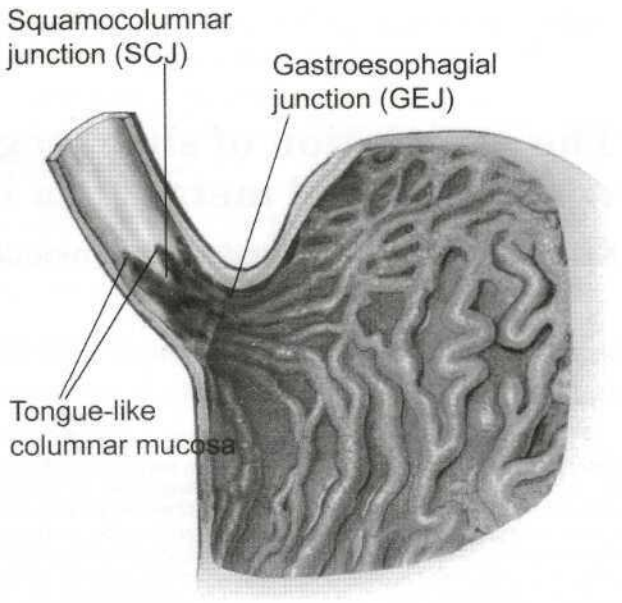


Figure 1. Schematic appearance GEJ, squamocolumnar junction (z-line) and tongue-like columnar protrusions.

MATERIALS AND METHODS

The study comprised 50 patients (32 male, 18 female; median age: 57 years, range 47-80) who had undergone upper endoscopy due to dyspeptic complaints and were found to have tongue-like columnar mucosal protrusions (<3cm long) above the GEJ. Exclusion criteria included the use of antibiotics and acid inhibitor drugs within 30 days of endoscopy, prior gastric or esophageal surgery and gastric cancer. The cases were not taken consecutively in the study. Details of gastroesophageal reflux symptoms were not evaluated.

Endoscopically, the GEJ is accepted to be the most proximal margin of the gastric mucosal folds (2,11) while the SCJ, is considered as the border between the esophageal squamous mucosa and gastric columnar mucosa which is located within 2 cm of the most proximal edge of gastric folds in the esophagus (2) (Figure 1). The measurements were made by the endoscope, with the incisor teeth as a reference point during endoscopy, which endoscopy was performed with the Fujinon FG-100FP endoscope (Fuji photo optical, Omiya City, Japan). All biopsy specimens were obtained with standard biopsy forceps. Patients whose metaplastic segments above the GEJ were >3 cm long were not included in the study. Also, patients with ulcers, erosion, stricture at the lower end of the esophagus, esophageal or stomach cancer, hiatal hernia or those who had undergone esophageal or stomach surgery were not included in the study.

The biopsy specimens were obtained as follows. Two biopsy specimens were taken from antrum >2 cm away from the pylorus, incisura angularis, corpus greater curvature and cardia and four biopsy specimens were taken from tongue-like columnar mucosal protrusions (<3cm long) above the GEJ. Gastric cardia biopsy specimens were obtained with the endoscope in a retroflexed position within a 2cm area below the GEJ.

The biopsy samples, formalin-fixed and embedded in paraffin, were stained with hematoxylin-eosine, HID-Alcian blue at pH 2.5 and modified Giemsa stain and evaluated by only one pathologist. The presence and activity of gastritis, intestinal metaplasia, and H. pylori were graded according to the updated Sydney System (12). *H.pylori* infection was investigated by urease, histopathological (modified Giemsa stain), and serological methods and a positive result in at least one of these meth-

ods was accepted as *H.pylori* positive.

In tissue samples taken from the esophagus and the stomach, the observation of goblet cells was considered to be sufficient for an intestinal metaplasia diagnosis. Cases in which sulphomucin was dominant and contained a lesser amount of sialomucin were diagnosed as colonic (incomplete) type IM, while those in which the goblet cells contained sialomucin were diagnosed as small-bowel (complete) type IM.

Data are expressed as mean ± SE. Differences between the SSBE (+) and SSBE (-) cases were analysed by chi-square test (Fisher's exact test). A $p < 0.05$ was considered to indicate a significant difference.

RESULTS

The demographic and histological findings of patients are shown in Table 1.

Intestinal metaplasia (or SSBE) at the tongue-like columnar mucosal protrusions above the GEJ was found in nine of 50 (18%) patients (Figure 2 and 3). The results of histopathological examination of the samples taken from the stomach showed that 42 (84%) of the cases had chronic gastritis, 14 (28%) had IM in different parts of the stomach (antrum five, incisura angularis seven, corpus one, antrum & cardia one), and two (4 %) had mild dysplasia (cardia). Out of the 50 patients included in the study, 32 (64%) were found to be *H.pylori* positive.

Short segment Barrett's esophagus showed a close association with chronic gastritis and *H.pylori* infection. While all cases (100%) with Barrett's metaplasia had chronic gastritis, *H.pylori* was found to be positive in five of them (55%). In six (66%), cases Barrett's metaplasia was accompanied by IM (two in the antrum, one in the antrum & cardia, three in the incisura angularis) in other parts of the stomach. In one case with Barrett's metaplasia, mild dysplasia was also detected in the cardia. All SSBE cases were over 50 years of age and the average age was 58.5±5 years.

Table 1. Comparison of SSBE (+) and SSBE (-) in tongue-like protrusions (<3cm long) above the GEJ

	SSBE (+) n=9 (%18)	SSBE (-) n=41 (%82)	p value
Mean age	58.5 ± 5	56.6 ± 7.2	NS
Male/Female	6/3	27/14	NS
H.pylori (+)	5(55%)	27(66%)	NS
Chronic gastritis	9(100%)	33(80%)	NS
IM in stomach	6(66%)	8(19.6%)	0.003*
Antrum	2(22%)	3(7%)	
Incisura angularis	3(33%)	4(9%)	
Corpus	-	1(2%)	
Antral & cardia	1(11%)	-	
Mild dysplasia (cardia)	1(11%)	1(2%)	-

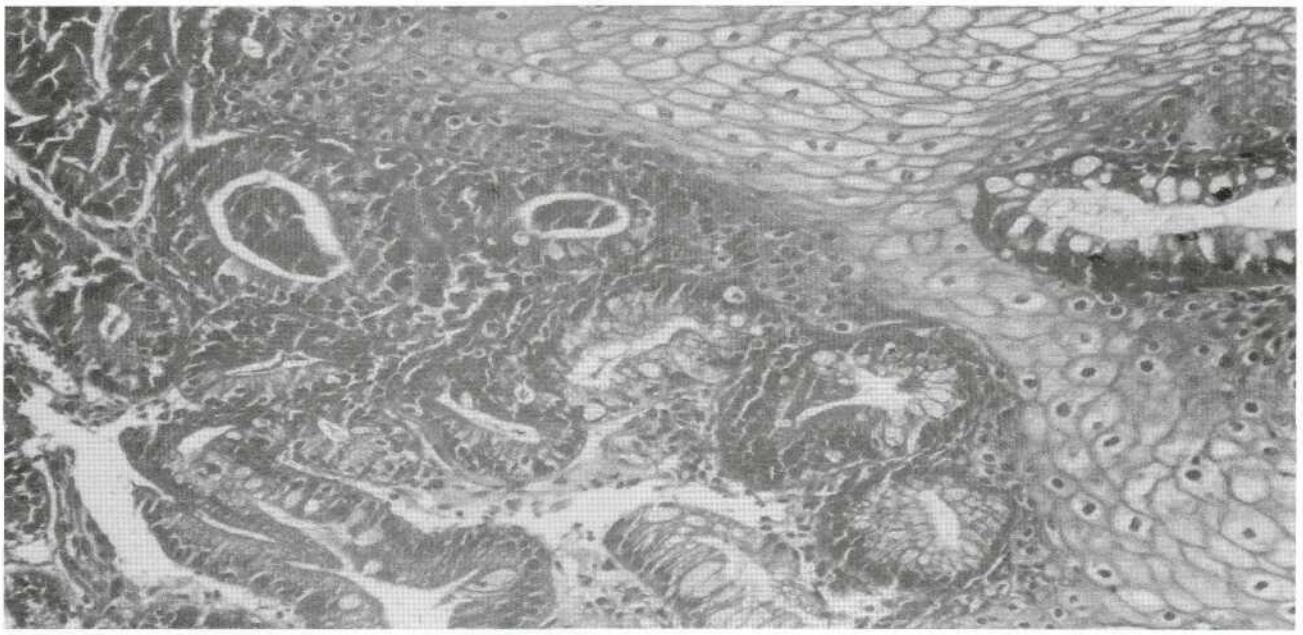
NS: not significant
*P < 0.01

Figure 2. Glandular structures consist of scarce goblet cells associated with mature squamous epithelium (Hematoxylin-eosin, X200)

Twenty-seven (64%) of the 42 cases not diagnosed with Barrett's metaplasia were found to be *H.pylori* positive. In eight (19.6%) of these cases, IM was detected in different parts of the stomach (four in incisura angularis, three in antrum, one in corpus), while mild dysplasia (in the cardia) was detected in one case.

DISCUSSION

In the western world, a steady increase in the incidence of adenocarcinoma of the esophagus and



Figüre 3. Goblet cells including sialomucin (blue stained) and sulphomucin (black stained) in material obtained from distal esophagus (HID-Alcian blue pH: 2.5, X 400)

esophagogastric junction (EGJ) has been observed. (13-15). Barrett's esophagus is a metaplastic condition in which columnar epithelium containing goblet cells replaces the squamous epithelium normally found in the esophagus. In most patients esophageal adenocarcinoma arises from its premalignant precursor lesion, Barrett's esophagus (2). In particular, specialized columnar epithelium (IM characterized by the presence of goblet cells) may progress through dysplasia to invasive adenocarcinoma (3). However, a recent meta-analysis has suggested that the mean annual incidence of esophageal cancer for patients with Barrett's esophagus is approximately 1% (16,17).

Short, tongue-shaped mucosal protrusions originating from the columnar epithelium in the GEJ were once considered normal, that the lower one-two cm of the esophagus was lined by gastric type columnar epithelium containing simple mucous glands (18). However, this view was completely changed after Spechler et al. (19) found goblet cells, specialized columnar epithelium in the GEJ, in patients without long segment Barrett's. This condition was called SSBE and was independently confirmed by numerous research groups (6,7,11,20). The cancer development risk in this condition is similar to that of LSBE (16).

The epidemiological characteristics of SSBE are different from IM detected in the GEJ (6,7). Intestinal metaplasia at a normal-appearing GEJ may be associated with IM of the stomach and infection with H. pylori, whereas SSBE in the distal esophagus is associated with GERD (6,21). Therefore, IM detected in tongue-like columnar mucosal protrusions above the GEJ should be differentiated from metaplasia that occurs just beneath an apparently normal appearing SCJ (6).

In this study, SSBE was detected histopathologically at the tongue-like columnar mucosal structures formed above the GEJ in nine (18%) of the total 50 cases. In one of the cases with Barrett's, we also detected mild dysplasia in the cardia.

The prevalence of IM around the SCJ has been found to be different in various studies. The prevalence of specialized columnar epithelium in those with a macroscopic columnar lining extending £1 cm, >l-2cm, >2-3 cm and > 3cm was found to be 18%, 36%, 38%, and 93% respectively (6). Cameron et al. (22) reported that the prevalence of IM was approximately 17% in biopsies taken from the area just distal to a normal z-line and 50% in tongue-shaped mucosal extending <3cm. Similarly, Trudgill et al. (23) found that the IM prevalence between the proximal ending point of the gastric folds and the SCJ was 20% in patients whose columnar epithelium was <1 cm long, and 30% in those where it was 2-3 cm long. However, Hackelsberger et al. (20) detected IM at the SCJ in

only 13% of patients undergoing upper endoscopy. In the same study they observed that IM was significantly associated with *H.pylori* infection and gastric IM. Csendes et al. (24) found the prevalence of IM to be 18% and 10.7% patients with GERD without esophagitis or with erosive esophagitis, respectively and that SSBE was three times more frequent than LSBE.

In this study, six (66%) of the cases with associated SSBE were found to have IM in different parts of the stomach. Moreover, all cases diagnosed with SSBE also had chronic gastritis. *H.pylori* positivity was found in five (55%) of the SSBE cases (Table 1).

There is no significant study regarding the association of Barrett's esophagus and IM in the stomach with *H.pylori* positivity. Weston et al. (25) however, noted a significant difference between the prevalence of intestinal metaplasia in esophagus and stomach of patients with Barrett's esophagus.

H.pylori colonization in the stomach may have a protective role in the development of Barrett's esophagus and its malignant complications (26,27). However, Peitz et al. (28) detected *H.pylori* in 50% of subjects, independently from the length of BE disease. This finding is concordant with the results of this study.

The association of the IM in the GEJ and its association with IM detected in various parts of stomach and H. pylori infection have been shown in various studies. Morales et al. (29), Mungan et al (30), Nandurkar et al. (11) and Hackelberger et al. (20) reported a significant association of IM at the GEJ and cardia with gastric IM and *H.pylori* positivity, whereas Trudgill et al. (23), Spechler et al. (18) and Vardar et al. (31) were not able to confirm these findings.

Some researchers have suggested a correlation between increasing age and IM and SSBE in the GEJ. Various surveys have shown that gender does not play a significant role either in the prevalence of IM a at the GEJ or in SSBE (6). All of the subjects in our study diagnosed with IM were over 50 years of age and the average age was 58.5±5 years.

It is now known that IM formed in the GEJ and SSBE may be responsible for the increase in adenocarcinoma originating from GEJ and distal esophagus (6,7). Specialized IM, detected in some of the biopsy samples taken from the distal esophagus or around the cardia, requires endoscopic and histological follow-up due to a malignant transformation risk. Endoscopic examinations should therefore, be made at intervals of three-six years (6).

In this study, the prevalence of IM was found to be 18 % at tongue-like columnar mucosal protrusions within the distal esophagus. These metaplastic changes showed an association with IM in other parts of the stomach and *H.pylori* infection. It is concluded that three is a need for larger and more comprehensive studies to investigate the presence of SSBE in tongue-like columnar mucosal protrusions (<3cm long) above the GEJ and to evaluate an association with *H.pylori* and IM seen in other of the stomach.

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