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The utility of cytokeratins 7 and 20 (CK7/20) immunohistochemistry in the distinction of short-segment Barrett esophagus from gastric intestinal metaplasia: Is it reliable?

Ozlem Kurtkaya-Yapicier¹, Rasim Gencosmanoglu*^{2,4}, Erol Avsar^{3,4}, Nadi Bakirci⁵, Nurdan Tozun^{3,4} and Aydin Sav¹

Address: ¹Department of Pathology, Marmara University School of Medicine, Istanbul, Turkey, ²Department of Gastrointestinal Surgery, Marmara University Institute of Gastroenterology, Istanbul, Turkey, ³Department of Gastroenterology, Marmara University Institute of Gastroenterology, Istanbul, Turkey, ⁴Sub-department of Gastroenterology, Department of Internal Medicine, Marmara University School of Medicine, Istanbul, Turkey and ⁵Department of Public Health, Marmara University School of Medicine, Istanbul, Turkey

Email: Ozlem Kurtkaya-Yapicier - okurtkaya@marmara.edu.tr; Rasim Gencosmanoglu* - rgencosmanoglu@marmara.edu.tr; Erol Avsar - avsar@superonline.com; Nadi Bakirci - nbakirci@marmara.edu.tr; Nurdan Tozun - nurdantozun@marmara.edu.tr; Aydin Sav - amsav@superonline.com

* Corresponding author

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Abstract

Background: The purpose of the present correlative immunohistochemical study was to assess the utility of cytokeratin (CK7 and CK20) expression in the diagnosis of short-segment Barrett esophagus, particularly its efficacy in differentiating Barrett mucosa from intestinal metaplasia of the gastric cardia and corpus.

Methods: Two groups of endoscopic biopsy specimens were examined, including 20 endoscopic biopsy specimens of short-segment Barrett esophagus (Group A) and equal number exhibiting *Helicobacter pylori* associated intestinal metaplasia of the gastric cardia and corpus (Group B). All were investigated by immunohistochemistry using the standard ABC method for CK7 and CK20 expression. Fisher's exact test was used for statistical analysis of Barrett CK7/20 and gastric CK7/20 patterns between the groups.

Results: The anticipated pattern of reactivity in Barrett mucosa (CK7: strong diffuse positivity in superficial and deep glands; CK20: positivity in surface epithelium and superficial glands) was seen in 2 cases of Group A specimens. The expected gastric pattern (CK7: patchy immunostaining with variable involvement of deep glands; CK20: patchy immunostaining of superficial and deep glands in incomplete intestinal metaplasia / absence of CK7 immunoreactivity with strong CK20 staining in superficial and deep glands in complete intestinal metaplasia) was seen in 8 cases of Group B specimens. The respective sensitivity and false-negativity values of CK7/20 staining for Barrett pattern in Group A were 10% and 90%, respectively. These values for gastric pattern in Group B were 40% and 60%, respectively. The specificity and false-positivity values of both patterns were same (100% and 0%, respectively). There was no statistically significant difference for Barrett pattern between the two groups ($P = 0.487$), while the observation of gastric pattern was significantly higher in Group B than in Group A ($P = 0.02$).

Conclusions: We concluded that these hypothesized and recently applied diagnostic criteria involving CK7 and CK20 immunoreactivity are not reliable in distinguishing short-segment Barrett esophagus from intestinal metaplasia as seen in gastric cardia and corpus.

Background

Barrett esophagus (BE) is associated with an increased risk of esophageal adenocarcinoma, a malignancy that has had a rapid rising incidence recently [1-3]. The etiology of BE is unknown, but genetic predisposition with ulcerative changes from gastro-esophageal reflux disease (GERD) might be responsible [4].

BE should be suspected at the endoscopy when the normal, whitish-appearing squamous epithelium is replaced by a red, velvety-appearing mucosa in the distal esophagus. The reliable diagnosis of BE is difficult related to sampling errors due to determination of the exact location of the gastro-esophageal junction such as in hiatal hernia. Diagnostic difficulties arise when the endoscopist deals with the short-segment BE. Junctional, fundic and specialized (intestinal) types of glandular epithelium were described for the definition of BE by Paull *et al.* [5]. But it was recently reported that the detection of the latter is a reliable criterion for the diagnosis of BE [4,6]. *Helicobacter pylori* (*H. pylori*) might be associated with carditis and intestinal metaplasia of the cardia [7]. Therefore, intestinal metaplasia involving the cardia related to *Helicobacter* gastritis can be histologically indistinguishable from intestinal metaplasia of the distal esophagus.

It has been suggested that cytokeratin subsets 7 and 20 (CK7 and CK20) might be useful to distinguish both long- and short-segment of BE from intestinal metaplasia of the proximal stomach [8-11]. The purpose of this study was to evaluate the cytokeratin (CK7 and CK20) expression in the diagnosis of short-segment Barrett esophagus, particularly its utility in differential diagnosis of Barrett mucosa from intestinal metaplasia of the gastric cardia and corpus.

Methods

Endoscopy specimens of the patients referred from Marmara University Institute of Gastroenterology were reviewed from the files of the Department of Pathology at the same university between 1998 and 2002. At least 4 biopsies were taken from irregular squamo-columnar junction (SCJ) with peninsulas or tongues of columnar epithelium and islands of squamous or columnar epithelium for each case. When more than one peninsula or tongue of columnar epithelium in the distal esophagus was observed endoscopically, 4 biopsies were taken from each peninsula and they were sent to histopathologic examination in separate eppendorph tubes. Small penin-

sulas with linear vessels distal to the SCJ and any focal abnormality were also biopsied.

Esophageal and gastric biopsies were taken antegrade or retrograde with retroflexion of the endoscope when it was necessary. The retroflexed approach was preferred for sampling of cardia. The cases which were diagnosed histopathologically as short-segment BE were included to the study. Short-segment BE was defined endoscopically as tongues less than 3 cm in length above the esophago-gastric junction (EGJ) with its resemblance to small intestine having well-formed microvilli and intestinal metaplasia either with hematoxylin and eosin (H&E) (Figure 1) or Alcian blue pH2.5 positive goblet cells (Figure 2) on microscopic examination.

The study group consisted of 20 patients with short-segment BE (Group A) and the equal number of patients with gastric intestinal metaplasia (cardia and corpus) accompanied by *H. pylori* gastritis (Group B). Biopsy specimens that were obtained within 5 mm distance below the EGJ were considered as cardiac mucosa.

Specimens were fixed in 10% buffered formalin and embedded in paraffin. Serial sections were cut from each specimen. All sections were stained with routine H&E stain. Periodic acid Schiff (PAS), Alcian blue pH 2.5 and Alcian blue pH 0.5 were used to identify neutral mucin, sialomucin and sulphomucin, respectively. Giemsa stain was used to reveal *H. pylori*. We excluded the cases without detected goblet cell metaplasia by Alcian blue stain for both Group A and Group B. *H. pylori* infection was confirmed with Giemsa stain for the cases in Group B.

Endoscopic biopsies were grouped as complete (type I) or incomplete (type II) intestinal metaplasia according to the previously defined criteria [12]. The proposed Barrett CK7/CK20 pattern (CK7: strong diffuse positivity in superficial and deep glands; CK20: positivity in surface epithelium and superficial glands) and gastric CK7/CK20 pattern (CK7: patchy immunostaining with variable involvement of deep glands; CK20: patchy immunostaining of superficial and deep glands in incomplete intestinal metaplasia / absence of CK7 immunoreactivity with strong CK20 staining in superficial and deep glands in complete intestinal metaplasia) were evaluated for all cases. Six control biopsies were constituted retrospectively from patients whose biopsies showed normal SCJ (n = 3) and normal cardia (n = 3) microscopically.

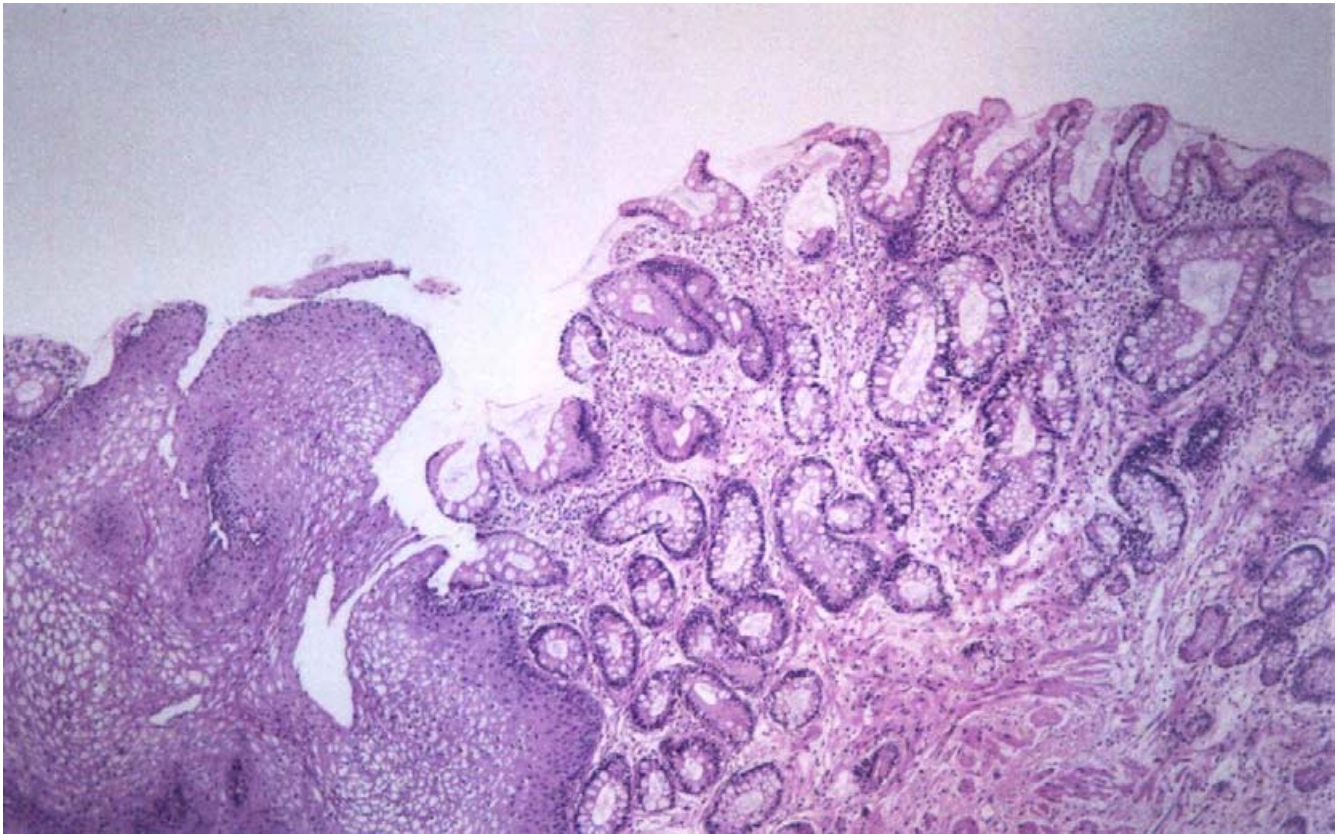


Figure 1
Section from gastro-esophageal junction showing BE with goblet cells, H&E, $\times 40$

Group A

Clinical data including age, sex, gastro-esophageal reflux symptoms, and endoscopic findings and short-segment Barrett mucosa were obtained from each case. The patients with BE within the last 3 cm of distal esophagus were included to the Group A. Patients with positive *H. pylori* were excluded from the study.

Group B

Clinical data including age, sex, gastro-esophageal reflux symptoms, endoscopic findings, and *H. pylori* status were obtained from each case. Patients with positive *H. pylori* were included to the study. Twenty endoscopic biopsies (cardia, $n = 9$ and corpus, $n = 11$) with histologic evidence of intestinal metaplasia were studied.

Immunohistochemical studies

One tissue block was selected for each case. The blocks were cut at 5 μm sections. Slides were deparaffinized and rehydrated through graded alcohols. Antigen retrieval was performed by using citrate buffer in microwave both for CK7 and CK20. Slides were incubated in 3% hydrogen

peroxide/methanol for 20 min to block nonspecific background staining due to endogenous peroxidase. Using the standard streptavidin-biotin peroxidase complex (ABC) method, CK7 (clone OV-TL 12/30, Neomarkers, Fremont, CA, USA) and CK20 (clone K20.4, Neomarkers, Fremont, CA, USA) were performed on all slides. The slides were incubated for 30 minutes in secondary antibody solution. Diaminobenzidine (DAB) served as the chromagen. The slides were counterstained with hematoxylin. The samples of breast carcinoma and colon carcinoma were used as positive controls for CK7 and CK20, respectively. Negative controls were produced with the same tumor samples and staining methods by omitting the primary antibodies.

Statistical Analysis

Fisher's exact test was used for analysis of Barrett and gastric patterns. A result was considered statistically significant if the *P* value was less than or equal to an alpha-level of 0.05.

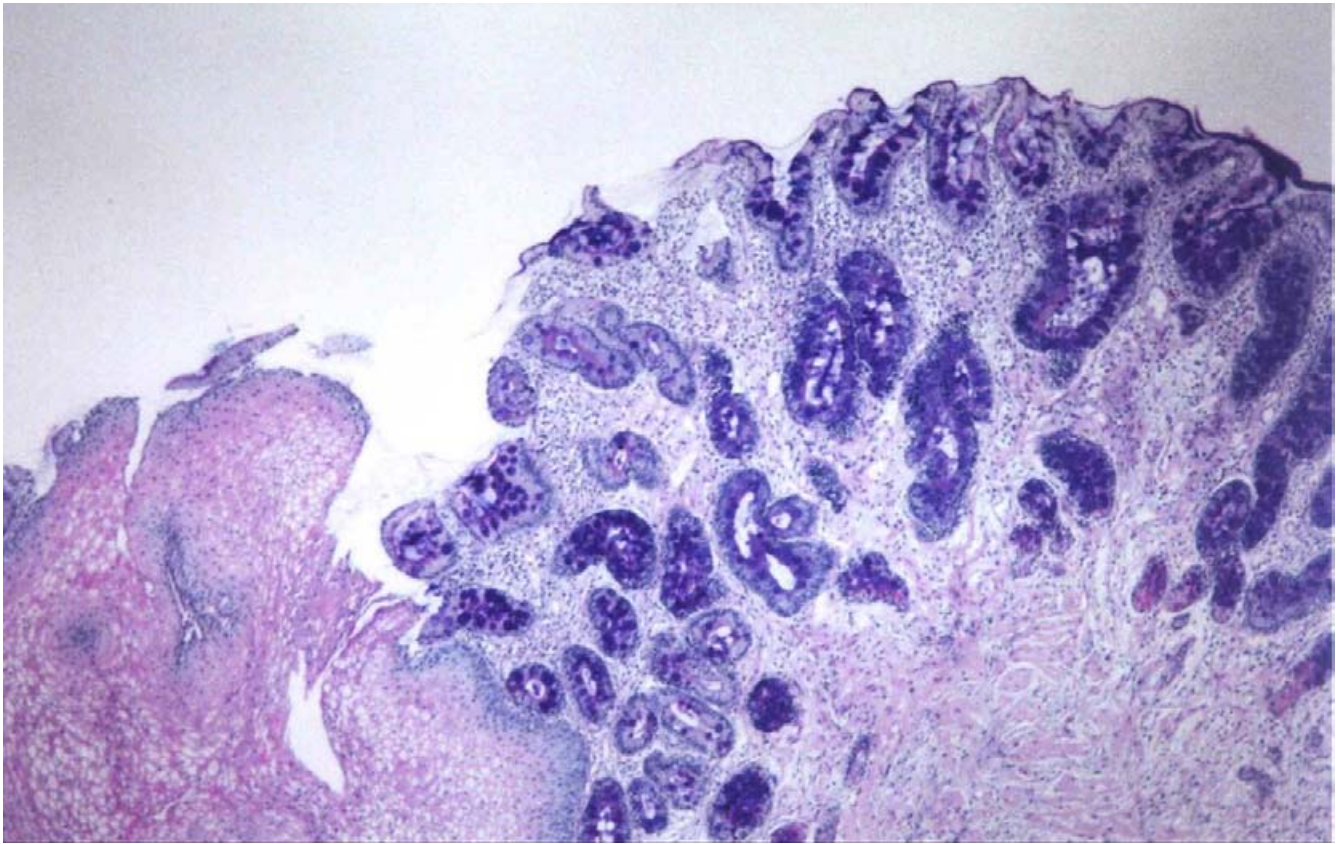


Figure 2
Intense blue staining of goblet cells with Alcian blue pH 2.5/PAS, ×40

Table 1: Clinical and immunohistochemical findings in patients with short-segment BE and gastric intestinal metaplasia

	Short-segment BE (n = 20)	Gastric intestinal metaplasia (n = 20)
Age (yr) ^a	28–77	25–73
Male/Female	4/1	2/3
Barrett CK7/20 pattern ^b (%)	10	0
Gastric CK7/20 pattern ^c (%)	5	40
Other patterns (%)	85	60

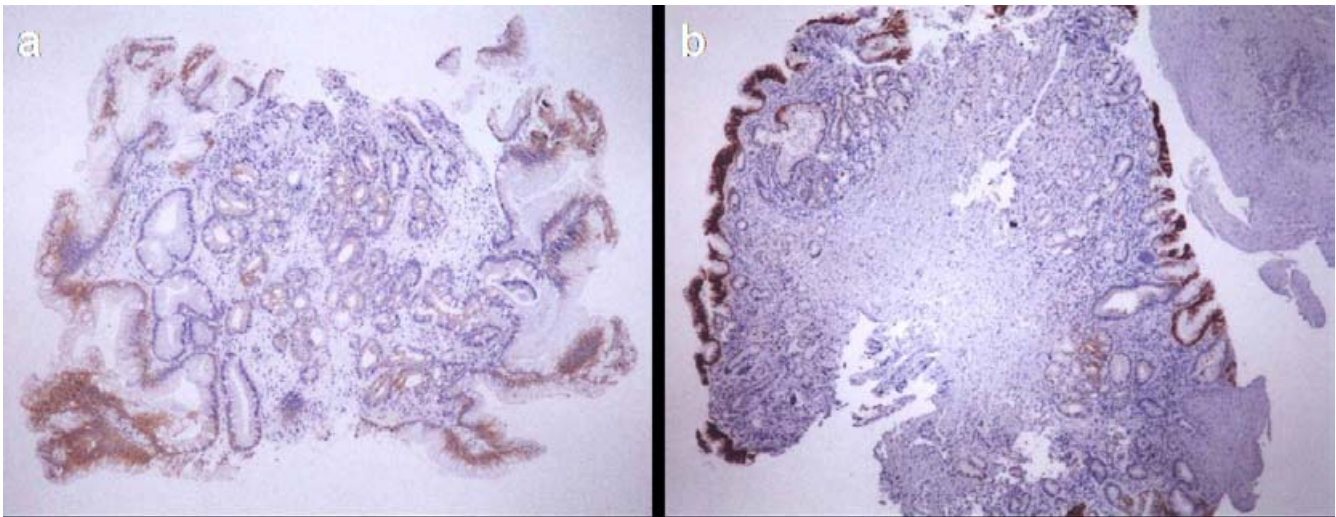
^a Range ^b Defined in reference #8 ^c Defined in reference #8

Results

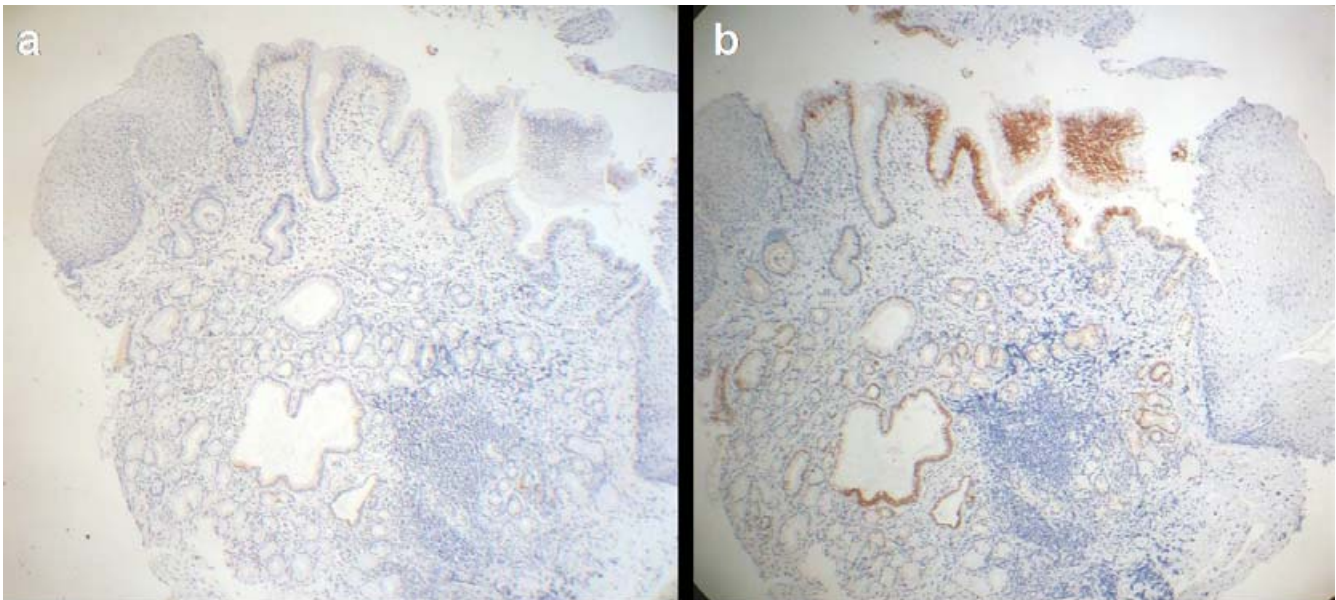
In total, 40 patients were included to the study. The median age of the patients was 46 (range, 28–77) years in Group A and 50 (range, 25–73) years in Group B. The male to female ratio was 4 to 1 in Group A, whereas it was 2 to 3 in Group B. The clinical and immunohistochemical features were summarized in Table 1.

Group A

Reflux symptoms were found in 14 cases (70%) with BE. High frequency of hiatal hernia (65%) was found in this group. Three cases showed low-grade dysplasia out of total. Thirteen cases revealed incomplete intestinal metaplasia and 7 cases were complete intestinal metaplasia by using Alcian blue stain. The anticipated Barrett CK7/20 pattern was identified only 2 of the 20 cases (Figure 3).

**Figure 3**

a. Diffuse moderate CK7 immunostaining of superficial and deep glands in BE, $\times 40$, **b.** Band-like CK20 immunostaining of surface epithelium and superficial glands in BE, $\times 40$

**Figure 4**

a. Absent CK7 immunostaining in BE, $\times 100$, **b.** Patchy CK20 immunostaining of superficial and deep glands in BE, $\times 100$

One case showed anticipated gastric CK7/CK20 pattern. The remainder had variable staining patterns; like no immunostaining ($n = 6$) or focal immunostaining ($n = 11$) for CK7 with focal or diffuse immunostaining for CK20, which did not fit in with the anticipated Barrett

CK7/20 pattern (Figure 4). The sensitivity, specificity, false-positivity, and false-negativity of CK7/20 staining for Barrett pattern were 10%, 100%, 0%, and 90%, respectively.

Group B

Eleven cases showed complete intestinal metaplasia, whereas 9 cases showed incomplete intestinal metaplasia by using Alcian blue stain. Eight cases expressed the gastric CK7/20 pattern (cardia, $n = 5$ and corpus, $n = 3$). Six of them showed complete and 2 incomplete gastric CK7/20 pattern. Barrett CK7/20 pattern was not observed in any patient with gastric intestinal metaplasia. The staining characteristics of the remaining 12 cases did not fit in with the anticipated gastric CK7/20 pattern; due to the patchy CK7 and/or focal CK20 immunopositivity in cases with complete intestinal metaplasia and absence of CK7 immunopositivity and/or diffuse CK20 immunopositivity in cases with incomplete intestinal metaplasia. The sensitivity, specificity, false-positivity, and false-negativity of CK7/20 staining for Barrett pattern were 40%, 100%, 0%, and 60%, respectively.

There was no significant difference for Barrett pattern between the two groups (2/20 in Group A *vs.* 0/20 in Group B, $P = 0.487$), while the observation of gastric pattern was significantly higher in Group B than in Group A (8/20 *vs.* 1/20, $P = 0.02$).

Normal SCJ showed patchy immunopositivity for CK7 without any immunoreactivity for CK20, but normal gastric cardia revealed immunonegativity for CK7 combined with patchy immunopositivity for CK20, which is limited to the surface epithelium.

Discussion

Intestinal metaplasia may develop in the cardia in patients either with short-segment BE or carditis especially caused by *H. pylori*. Distinction between these two entities is important since the etiology and risk of developing adenocarcinoma are different [7]. BE is believed to be caused by GERD and associated with an increased risk of esophageal adenocarcinoma [1,2,4]. Microscopically, BE can be defined as replacement of the esophageal squamous epithelium by metaplastic specialized (intestinalized) columnar epithelium. Other epithelial types are junctional type and fundal type of epithelia. The diagnosis of BE requires biopsy confirmation of intestinal metaplasia with Alcian blue pH2.5 positive goblet cells in addition to typical endoscopic findings. The exact level of SCJ, proximal aspect of the gastric folds, and linearly oriented mucosal vessels in the distal esophagus and EGJ should be identified [13]. SCJ normally corresponds to the proximal margin of the linear gastric folds which means EGJ. The small vessels oriented parallel to the long axis of the esophagus disappear at the normally located SCJ. However, detection of abnormal extension of these vessels below the SCJ and above the proximal margin of gastric folds is an evidence of the presence of columnar epithelium in the distal esophagus [14].

Distinguishing BE from other entities which may render similar histopathologic features is paramount. Because of no absolute histological criteria for diagnosing Barrett mucosa has been established yet, recent studies [8-11,15-19] mainly depend on patterns of some cytokeratin subsets, especially two distinct patterns of CK7/20 staining. Cytokeratins are highly conserved polypeptides and represent a group of cytoskeletal structural proteins present in all epithelia. There are at least 20 distinct forms of cytokeratins in epithelial cells and variable patterns of expression depending on the type, location, and differentiation of the epithelium [20]. CK7, essentially, is not expressed in normal epithelium of the gastrointestinal tract, whereas CK20 is expressed in intestinal epithelium, gastric foveolar epithelium, and endocrine cells in the upper portions of the pyloric glands. Barrett CK7/20 pattern was first defined by Ormsby *et al.* [8] as staining of the superficial epithelium for CK20 and staining of both superficial and deep metaplastic epithelium for CK7. The designated gastric CK7/20 pattern was grouped into two patterns regarding the type of the intestinal metaplasia (incomplete/complete) by the same authors. According to their suggestion, patchy CK7 expression with variable involvement of deep glands was seen in incomplete gastric intestinal metaplasia, whereas strong CK20 expression in superficial and deep glands with the absence of CK7 expression was seen in complete gastric intestinal metaplasia. In this pioneering study, Barrett CK7/20 pattern was highly sensitive and specific when compared to cases with gastric intestinal metaplasia. However, *H. pylori* status of the cases was not mentioned. Studies by Glickman *et al.* [9] and Jovanovic *et al.* [15] confirmed Ormsby's findings in 91% and 94% of their cases with long-segment BE, respectively. On the other hand, studies by some other researchers have not been able to support Ormsby's findings; the proposed Barrett CK7/20 pattern was found in 54% of patients with long-segment BE by Mohammed *et al.* [16] and only 39% of patients with long-segment BE by El-Zimaity *et al.* [17].

Ormsby *et al.* [11] later assessed the utility of CK7/20 patterns in short-segment BE in another study and found that "diagnostic" Barrett CK7/20 pattern was present in 82% of patients with short-segment BE. Although Mohammed *et al.* [16] found almost the same percentage (81%) for the short-segment BE cases with Ormsby *et al.* [11], they found the same pattern in 30.7% of patients with intestinal metaplasia in cardia and more interestingly in 55% of biopsies which had either normal or inflamed gastric mucosa without intestinal metaplasia.

In the present study, 10% of patients with short-segment BE showed the anticipated CK7/20 pattern and 40% of patients with gastric intestinal metaplasia showed the anticipated gastric CK7/20 pattern with appropriate complete or incomplete intestinal metaplasia. The sensitivity

of Barrett CK7/20 pattern was very low (10%) in the BE group despite its high specificity (100%). The sensitivity of gastric CK7/20 pattern was also low (40%) in gastric intestinal metaplasia group, although the specificity was high (100%) in this group as well. Gastric CK7/20 pattern was significantly higher in gastric intestinal metaplasia group than in BE group ($P = 0.02$), whereas Barrett CK7/20 pattern did not significantly differ between the two groups ($P = 0.487$). Based on these results, to use two distinct patterns of CK7/20 staining could not be accepted as a reliable method in differentiating short-segment BE from gastric intestinal metaplasia since both patterns have very low sensitivity and very high false-negativity values.

In the Couvelard's study [10] 31% of patients and in the Ormsby's study 15% of patients with short-segment BE associated with Barrett CK7/20 pattern had *H. pylori* infection. Although the percentage of the positive *H. pylori* cases in patients with short-segment BE associated with a Barrett CK7/20 pattern was not mentioned in the Mohammed's study [16], 6% of patients had *H. pylori* infection with short-segment BE. Since intestinal metaplasia may be seen both in *H. pylori* infection and BE, combination of these entities should not be of the interpreted for evaluating the utility of the cytokeratin subsets. We excluded the *H. pylori* positive cases even if it was diagnosed as BE. Therefore, the differences between our study and previously reported results may have been due to this strict distinction of *H. pylori* positive BE cases in the present study. Differences in biopsy protocols between previous studies and the present study (number, size or site of the specimen, anterograd or retroflexed approach) might have been another reason for differences in the results. To identify the exact location of the cardia anterograd approach should be used. However, regarding the normal cardiac epithelium, its existence remains still unclear, since the results of different studies are contradictory [21-23]. While the two studies suggest that normal cardiac epithelium represents a form of metaplastic epithelium secondary to gastro-esophageal reflux [21,22], another study reported by Kilgore et al suggests that cardiac mucosa exists as a native structure [23]. Further studies may provide information on the cardiac mucosa, especially its' relation with reflux changes and BE.

Conclusions

On the basis of our results, we are less confident of the use of the proposed CK7/20 patterns for differentiating short-segment BE from gastric intestinal metaplasia. It is important to recognize the endoscopic features that aid the diagnosis of BE for endoscopists, since the histology of intestinal metaplasia in cardia related to other etiologies and Barrett esophagus is identical. We suggest that the definition of BE should be based on the clinic, endoscopic,

and histological findings rather than the pattern of CK7/20 immunostaining.

List of abbreviations

BE: Barrett Esophagus

GERD: Gastro-Esophageal Reflux Disease

H. pylori: *Helicobacter pylori*

CK7: Cytokeratin 7

CK20: Cytokeratin 20

SCJ: Squamo-Columnar Junction

EGJ: Esophago-Gastric Junction

H&E: Hematoxylin and Eosin

PAS: Periodic Acid Schiff

ABC: Standard Streptavidin-Biotin Peroxidase Complex

DAB: Diaminobenzidine

GEJ: Gastro-Esophageal Junction

Competing interests

None declared.

Authors' contributions

OK-Y planned the study, performed the histopathologic evaluation and prepared the manuscript. RG participated in the endoscopic procedures and the redaction of the article. EA and NT participated in the endoscopic procedures. AS participated in the histopathologic evaluations. RG and NB performed the statistical analysis. All authors read and approved the final manuscript.

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