Review Article

Association of Barrett's esophagus with non-goblet esophageal columnar epithelium: appraisal of the surrounding controversies

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Abstract: Barrett's esophagus (BE) predisposes to esophageal adenocarcinoma (EAC) and significantly increases its incidence. However, the precise diagnostic criteria of BE are not consistent internationally. The definition of BE is still controversial because two types of metaplastic epithelia have been identified: goblet-cell columnar epithelium (GCE), and non-goblet-cell columnar epithelium (NGCE). The identification of goblet cells, which is currently a prerequisite for the diagnosis of BE according to the American college of gastroenterology (ACG), may not be a sensitive indicator for the evaluation of neoplasia risk in these patients. We discuss the most recent advances in understanding the relation between BE and NGCE, as well as the key molecular features of malignancy in these patients. There exists a lack of international consensus at this time on whether to include non-goblet metaplasia in the definition of BE.

Keywords: Barrett esophagus (BE); non-goblet cells epithelium; goblet-cells epithelium; intestinalization; esophageal adenocarcinoma (EAC); metaplasia

Submitted Mar 10, 2013. Accepted for publication Apr 25, 2014.
doi: 10.3978/j.issn.2224-4778.2014.04.06
View this article at: http://dx.doi.org/10.3978/j.issn.2224-4778.2014.04.06

Introduction

Barrett's esophagus (BE) predisposes to esophageal adenocarcinoma (EAC) and significantly increases its incidence (1). EAC has significantly increased in Europe and North America, and currently accounts for approximately 70% of esophageal malignancy (2). The early detection of this neoplastic process is essential, considering its poor prognosis (3). However, the precise diagnostic criteria of BE are not consistent. Some groups required long-segment (≥3 cm) of columnar epithelium for the diagnosis, to overcome uncertainty of the gastro-esophageal junction (GEJ) location, and extension of normal cardiac mucosa (CM) (4-6). Later, short segment BE was also found to have increased risk of AC (7).

In addition, the presence of goblet cells was considered to be essential for the diagnosis of BE. This emanated from the association between intestinal metaplasia (IM) and EAC (8). However, there is no universal consensus whether goblet metaplasia should be a requirement for the diagnosis of BE (9).

Goblet cell IM increases the risk of EAC. However, the implications of non-goblet cells columnar epithelium (NGCE) remain an area of ongoing research. Although the role of NGCE has been reviewed in the past (10), in this article, we review the most recent advances in delineating the relationship between NGCE and BE.

Columnar epithelium at the distal end of esophagus

Two theories exist regarding the columnar epithelium between the esophagus and the stomach. Some experts have considered that the presence of any esophageal columnar epithelium is a reflux-related abnormality (4,11). Alternatively, others suggested that this epithelium represents a buffer zone called the cardia, and its length ranges from 4 mm to 2 cm. Allison *et al*. differentiated the columnar epithelium belonging

to the esophagus versus the stomach by finding esophageal submucosal glands (12). A recent systematic review by Lenglinger *et al*. suggested that abandoning the term "cardia" to describe the proximal stomach may be justified (6,13,14). We focus on reflux-related conversion of squamous to columnar epithelium at the distal end of the esophagus and its relationship to neoplasia.

The BE phenotype may be better than squamous epithelium to protect against exposure to refluxed acid and bile. However, the BE phenotype has approximately 100 times increased risk of AC compared to that of the general population. Indeed, trends of increased risk of malignancy at the gastric cardia have been reported in certain populations (15).

There exists three types of esophageal columnar epithelium (I) CM, composed of mucus glands without parietal cells; (II) oxynto-cardiac, a fundic-type mucosa (FM), composed of chief and parietal cells; and (III) IM, composed of specialized-type with intestinal features including villiform surface and mucus glands with goblet cells (4,16). NGCE refers to CM and FM (4,16). Currently, it is thought that AC rises from IM (17,18).

Another important concept is the multilayered epithelium that was first described in BE in 1997 (19). A prospective study by Shields *et al*. evaluating the relationship between the multilayered epithelium and BE demonstrated a strong association with IM. This association was not apparent with NGCE in the acquired specimens (20).

What is non-goblet columnar epithelium?

Intestinalization features were studied in NGCE, wherein intestinal mucosal protein expression (Sucrase-isomaltase, and dipeptidilpepidase IV), as well as CDX-2 expression were demonstrated (21-24). Intestinal markers expression was studied in non-goblet cells containing tissue from NGCE *vs*. BE *vs*. normal control groups, and the NGCE group showed intestinal differentation (22). This differentiation was found to be increased in areas lacking goblet cells adjacent to IM areas in the BE group. Previous data supported the metaplasia theory involving transition from squamous epithelium to NGCE, followed by IM (16,25,26). Kerkhof *et al*. showed that CDX-2 expression in NGCE biopsies increases the likelihood of finding goblet-cells in follow-up biopsies (27). In a human model of GERD studied in remnant esophagi following esophagectomies and gastric preservation, Castillo *et al*. discussed the role of non-goblet columnar metaplasia as well as molecular parameters such as BMP4 and CDX2. The authors concluded that BMP4 activation in non-goblet metaplastic epithelium, as well as early expression of CDX2 are involved in the differentiation of BE (28). A recent review by Moyes *et al*. concluded that the dogma of "no goblet cells implies no cancer risk" cannot be accepted based on literature review. The lack of IM cannot imply the safety of excluding these patients from surveillance (29).

Mokrowieska *et al*. studied p16 tumor suppressor gene alterations in EAC. The authors found p16 mutations in BE gastric metaplasia. These findings support the theory that metaplastic non-goblet columnar epithelium of the esophagus may have neoplastic potential (30). In a different study, the authors also demonstrated lower liver-intestine (LI)-cadherin expression in poorly differentiated EAC, which could be caused by loss of the ability to produce goblet cells in advanced cases (31). Conversely, a recent study by Chandrasoma *et al*. concluded that with a systematic biopsy protocol of columnar-lined esophagus (CLE), patients could be separated into those with and without IM in such a manner as to overcome the possibility of false-negative diagnosis of IM. When IM is absent using that protocol, the patient is at no or extremely low risk of dysplasia and cancer. They concluded that inadequate sampling is a powerful confounder of why a near absolute association between IM and AC is not seen in other studies (32).

Molecular markers of intestinal differentation in the esophagus

The caudal-related homeodomain transcription factors CDX1 and CDX2 are normally expressed exclusively in intestinal epithelia, playing important roles in proliferation and differentiation of these epithelial cells (33). The apical sodium-dependent bile acid transporter (ASBT) is expressed abundantly n in the ileum and mediates bile acid absorption across the apical membranes. Ectopic expression of CDX1, CDX2, and ASBT occurs in BE. Based on a recent study by Ma *et al*., it was hypothesized that ASBT gene expression is regulated by CDXs. The main inducers of CDXs expression are bile and acid reflux. Previous studies discussed how BE phenotype may be better than squamous epithelium to protect against refluxed acid and bile albeit increasing EAC risk (34,35). Eda *et al*. demonstrated that expression of CDX-2 precedes other intestine-specific genes in gastric IM, and may trigger it. Similar results were obtained in BE using reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry (36).

In animal models, it has been shown that acid reflux increased CDX-2 expression in the esophageal squamous epithelium (37). Later, human models of GERD showed that early expression of CDX2 are involved in the columnar epithelial differentiation of BE (28). This expression starts during esophagitis, and CDX-2 is perceived to be a trigger of BE (38). The authors relied on intestinal gene expression for BE diagnosis and not histologic characteristics. Therefore, they did not differentiate between GCE and NGCE. They reported 87% concordance between this molecular diagnosis and the traditional histological diagnosis of IM.

CDX-2 expression has been suggested as a marker of BE when unequivocal goblet cells cannot be identified (21,23). Colleypriest *et al*. showed that CDX-2 was observed not only in goblet columnar epithelium, but also in non-goblet columnar epithelium and inflamed esophageal squamous epithelium (39). Recent study by Khor *et al*. found weak and focal CDX-2 expression in non-goblet columnar epithelium, suggesting that non-goblet columnar epithelium in BE may show features of intestinalization (40).

Vallböhmer *et al*. quantitatively measured CDX-2 mRNA isolated from different epithelial types in patients with GERD symptoms and found stepwise increase in gene expression starting at squamous epithelium, followed by NGCE (40-70 times), leading to BE (400 times). These results support the two-step theory of esophageal IM. They concluded that CDX-2 may be a potential biomarker to detect the early transition to BE (41). Makita *et al*. studied the expression of CDX-2 and its methylation in BE and EAC. They discovered that CDX-2 expression was restored in poorly-differentiated invasive AC. CDX-2 reactivation did not correlate with differentiated intestinal phenotype (42). Interestingly, proton pump inhibitors was associated with regression of BE, and decreased mean extent of CDX-2 staining (43).

The dysplasia-neoplasia spectrum

Less-differentiated goblet cells have been found to give rise to neoplasia (44). AC is thought to arise from IM (17,18). Kelty *et al*. reviewed surveillance biopsies, taken over a 14-year follow-up, and did not report significant carcinoma rate differences in BE *vs*. NGCE, respectively (37% *vs*. 30%, P=NS) (45). Similarly, Gatenby *et al*. reported that the majority of patients who present initially with NGCE will develop IM on follow up (46). There was no significant difference in dysplasia or AC rates in goblet-cells versus non-goblet cells containing biopsies. These studies suggested that goblet cells are not a sensitive marker for increased neoplasia risk.

Furthermore, Chaves *et al*. studied the expression of gastric (MUC5AC and MUC6) and intestinal (MUC2) mucin markers in NGCE, GCE, and neoplastic cells. MUC6 was identified in NGCE as expected. However, it was also detected in neoplastic cells, and in GCE adjacent to neoplasia but not in GCE without neoplasia. The authors concluded that malignancy is not exclusively associated with the presence of intestinal differentiation (i.e., goblet cells) (47). In a different study, Takubo *et al*. (44) examined the epithelium adjacent to esophageal AC. The rate of exclusively finding NGCE epithelium immediately adjacent to neoplasia was higher than that of GCE (71% *vs*. 22%, respectively). They concluded that neoplasia arises in NGCE more frequently than IM, and thus the diagnosis of BE should not be restricted to the presence of goblet cells. This study, however, did not determine whether BE developed during follow-up. Later, the authors stated that 57% of patients had goblet cells (44).

The risk of neoplasia progression in NGCE and IM is also suggested by several molecular findings. Data have shown that DNA aberrancies that correlated with neoplastic progression of BE (48,49). Liu *et al*. studied these variables in NGCE, and showed that they occur equally in NGCE and IM (50). Moreover, the authors showed that goblet cells density in BE does not correlate with DNA alterations. They concluded that NGCE and GCE portend similar neoplastic potential. These aforementioned studies have several limitations, namely their cross sectional and retrospective nature.

Recent findings by Fassan *et al*. showed that microRNA dysregulation starts early in morphogenesis of Barrett's mucosa (BM) and plays a role in its columnar metaplastic transformation. These dysregulations are also responsible for both intestinalized and non-intestinalized metaplasia, supporting consistent biological change in the course of metaplasia irrespective of the presence of goblet cells (51). A recent study by Dias Pereira *et al*. followed patients with columnar lined esophagus without IM for a mean follow-up of 7 years. Patients were significantly younger (28.6 *vs*. 60 years, P<0.0001) and accounted for 48% of patients aged <40 years in the two cohorts, but only 1% of those aged >40 years (P<0.001). IM was documented in 60% of the cohort after a mean follow-up of 7 years. The authors concluded that columnar lined esophagus without goblet cells appears to be an intermediate step between squamous

and intestinal lining of the esophagus, and that this entity cannot be considered without risk for AC (52).

Future venues

The ACG defines BE as "a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have IM on histology" (53). The British Society of Gastroenterology does not mandate the identification of IM to establish the diagnosis of BE. Hence, the presence of columnar-lined mucosa with goblet cells is not an absolute requirement for the diagnosis of BM in their view (54,55). Similarly, the Japanese Esophageal Society defines BE as CLE that is continuous from the stomach and does not require the histological evidence of IM for diagnosis (56). Despite the ACG definition of BE, recent reports recommended the exclusion of IM from the definition of BE (57). More recent studies found that IM represented less than 5% of 826 consecutive esophageal biopsies, and the remainder lacked IM (58). BE adenocarcinoma (AC) is on the rise in other Asian countries such as Japan. Further research is needed to develop surveillance program for BE that takes in consideration the different mechanisms of onset and development, as well as the aforementioned differences in diagnostic criteria (56). To optimize and standardize the endoscopic assessment of BE, three main classification systems using combined magnification endoscopy (ME) and narrow-band imaging (NBI) (ME-NBI) have been proposed (Kansas, Amsterdam, and Nottingham). These are all based on mucosal morphology and have been claimed to predict histology within the BE (59-63). However, recent reports demonstrated several limitations to these available systems in terms of accuracy for the detection of IM, and identification of dysplastic BE, irrespective of the technique experience. Reports concluded that even ME-NBI technique is used and current classification systems are followed, they cannot replace random and targeted biopsies for histologic correlation (63,64).

Most comments about NGCE neoplasia risk are based on latest studies. One of the most recent studies regarding the risk of malignancy in the setting of IM versus the absence of IM has been presented by Bhat *et al.* (1). In this study, 8,522 patients with BE were followed between 1993 and 2008. BE was defined as columnar lined epithelium of the esophagus with or without IM. BE increased risk of cancer when IM was present versus when only columnar cell change was identified. Neoplasia does not arise from a goblet cell but from a more undifferentiated precursor cell, a recent review concluded. The authors stated that there appears to be a tendency for carcinomas in short segment BE to develop from areas with cardia-like mucosa, and that goblet cells could be detected with further follow up (65).

Conclusions

Others have thought of NGCE as an abnormality without need for treatment due to very low cancer risk (similar to asymptomatic arterial plaques in the cardiovascular system) (13). Based on latest research, the annual cancer risk for NGCE been reported to be 0.07% (1). Studies show that NGCE may be a transition between squamous and intestinal epithelia, provoked early by esophageal injury, and the risk of developing goblet cells increases with continued injury. NGCE may still display alarming factors of neoplasia (e.g., DNA changes) even without goblet cells on histology. Moreover, features other than goblet cells may better define intestinalization. Future studies are required to recognize additional non-histologic features of intestinalization, as well as recognizing the degree of intestinalization.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Bazerbachi F, Al Ustwani O, Gupta N, Reza Kermanshahi T. Association of Barrett's esophagus with non-goblet esophageal columnar epithelium: appraisal of the surrounding controversies. Transl Gastrointest Cancer 2014;3(3):114-120. doi: 10.3978/j.issn.2224-4778.2014.04.06

