Barrett’s esophagus: filling the gap

F. M. Riegler

Dear Readers,

We care about Barrett’s esophagus (BE), because it is a premalignant condition [1]. BE develops as a consequence of gastroesophageal reflux: the squamous lined mucosa of the normal esophagus is replaced by a columnar epithelium. Via a sequence involving low- and high-grade dysplasia, BE may progress toward the adenocarcinoma of the esophagus, the frequency of which dramatically increased in North America, Europe, and Asian countries within the last 20 years [1].

By definition BE is a columnar lined esophagus with intestinal metaplasia, this is columnar epithelium containing goblet cells. In keeping with the recent works by Paull et al. [2] from Boston and Chandrasoma [3] from Los Angeles non-dysplastic columnar-lined esophagus includes cardiac mucosa (mucus cell only epithelium), oxyntocardiac mucosa (mixture of mucus and acid producing parietal cells), and intestinal metaplasia (cardiac mucosa with goblet cells, this is Barrett’s esophagus) (Fig. 1A–C). The group around the Bostonian pathologist Robert Odze included the fourth type of non-dysplastic columnar-lined esophagus: multilayered epithelium, which represents a multi-layered mixture of squamous and columnar epithelium [4].

Conceptually, repeated gastric over-distentions (over eating) extend into the distal esophagus [5]. Over time the dilation of the esophagus becomes permanent and shortens the high-pressure zone at the esophagogastric junction (i.e., anti-reflux barrier) [3]. Due to impaired function of the esophagogastric junction high-pressure zone and reflux-induced formation of CLE the distal esophagus resembles the proximal stomach during endoscopy: this is the dilated distal esophagus, which is frequently attributed to the stomach and mistaken as hiatal hernia [3]. Recent studies show that the dilated distal esophagus is exposed to a pH less than 4.0 for 80–95% of the time [6].

Therefore, in patients with gastroesophageal reflux, CLE is interposed between the squamous-lined esophagus and the oxyntic mucosa of the proximal stomach (with straight tubular glands containing parietal, chief cells; CLE contains lobulated glands) [7]. This is the squamo-oxyntic gap, a term coined by the pathologist Para Chandrasoma. The proximal portion of the squamo-oxyntic gap may be visible during endoscopy, this endoscopically visible CLE, the length of the CLE covering the dilated distal esophagus (i.e., the cardia) can be assessed by multi-level biopsies obtained from the proximal portion of the endoscopically visible “gastric type folds” [3, 7].

The proximal to distal distribution of the mucosal types within the squamo-oxyntic gap follows a specific zonation with intestinal metaplasia at the squamo-columnar junction followed by cardiac and oxyntocardiac mucosa more distally [2, 3, 7]. According to the surgeon Steven DeMeester, Los Angeles, this zonation is paralleled by the pH gradient and the genetic profile gradient across the squamo-oxyntic gap [8] (Fig. 2). CDX2 and Sonic Hedgehog pathway mediate the formation of goblet cells and parietal cells, respectively. Alkaline and acidic pH activate the CDX2 and Sonic hedgehog pathway, respectively. During reflux the lumen of the proximal segment of the squamo-oxyntic gap is increasingly exposed to an alkaline pH, whereas the distal segment of the gap is exposed to acidic pH. As a consequence, goblet cell containing intestinal metaplasia develops at the squamo-columnar junction and parietal cell containing oxyntocardiac mucosa develops within the distal portion of the squamo-oxyntic gap [8].

Increased length of columnar lined esophagus (CLE) is associated with an increased risk for BE, dysplasia, and carcinoma [9]. However, recent evidence indicates the presence of BE within shorter segments of CLE, an observation which may be related to the life style (eating habits, obesity), the use of proton pump inhibitors, unknown genetic factors, and increased diagnosis of BE due to meticulous biopsy sampling during routine endoscopy of the esophagus. Remains the possibility that the milieu responsible for the development of BE, dysplasia, and cancer does not only depend on the luminal content. Using an in vivo animal model of gastroesophageal reflux, the group around Stuart Spechler and Rhonda Souza indicated the participation of complex immune responses in the development of esophagitis including bone marrow-derived stem cells [9]. CLE seems to result from a complex reflux-induced neurohumoral orchestration including immune-, nerve-, muscle-, and connective tissue cells (fibroblasts and myofibroblasts) and mediators released from these cells. This “cocktail of mediators” forms the micro-milieu, which mediates the symptoms and formats the genetic program of the stem cells within the esophageal epithelium [8, 9]. Thus the micro-milieu contributes to define the cellular composition of the columnar lined epithelium.
esophagus (Fig. 3). Pointing out the massive reflux-induced stress of the esophageal mucosa, recent studies revealed comparable genetic abnormalities within CLE without and with goblet cells [10]. Therefore, any CLE with malignant potential is now considered as Barrett’s esophagus [9]. Therefore logical treatment would consider the elimination of the reflux (effective anti-reflux surgery) and removal of the entire “target tissue” involved in the dysplasia/cancer development – i.e., the columnar epithelium and the subepithelial “neurohumoral orchestra” – by radiofrequency ablation.

The risk for those with BE to develop cancer is reported to be 0.5% per year [11]. When considering inter-observer variation regarding the histopathologic diagnosis of low- and high-grade dysplasia, the fact that dysplasia is associated with cancer in up to 50% of the cases and the contribution of the biopsy sampling error [8, 9], those with low- and high-grade dysplasia should be categorized within the “cancer group”. Then the risk for those with BE to develop cancer reads 5.3% per year [11]. The consequence of these discrepancies is twofold: let us eliminate BE before it becomes complicated for the physician and dangerous for the patient: before the de-

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**Fig. 1:** Histopathology of non-dysplastic columnar-lined esophagus. (A) transition from squamous (Squ) to cardiac mucosa (CM). Green arrow marks the squamo-columnar junction. (B) oxyntocardiac mucosa, green arrow marks a parietal cell. (C) Intestinal metaplasia, red arrow marks a goblet cell (H&E stains, courtesy of Prof. Dr. Fritz Wrba and Dr. Ildiko Mesteri, Pathology Department, Medical University of Vienna)

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**Fig. 2:** Correlation of endoscopy, histopathology (histo), luminal pH and the expression of CDx2 and sonic hedgehog (SHH) along the distal esophagus. Note endoscopically visible columnar lined esophagus between the squamo-columnar junction (SCJ) and the level of the rise of the gastric type folds (yellow arrow). IM: intestinal metaplasia; CM: cardiac mucosa; OCM: oxyntocardiac mucosa. The base of the triangle indicates the site of the maximal expression of the respective gene. Histopathology, CDx2- and SHH expression follow a pH-dependent gradient, as described in the text (according to Steven DeMeester [8]). Endoscopic image obtained with Olympus "technology.

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**Fig. 3:** Retrograde endoscopic view towards the esophagogastric junction and a biopsy site 1 cm distal to the level of the rise of the gastric type folds (A), cartooned in (B), with respective histopathology in (C). Histopathology shows columnar lined esophagus with intestinal metaplasia (red arrow marks a goblet cell) surrounded by oxyntocardiac mucosa (green arrows mark parietal cells). The adjacent location of intestinal metaplasia next to oxyntocardiac mucosa is suggested to result from the complex micro-milieu within the mucosa, as described in the text. Rise of ruga: level of the rise of the endoscopically visible gastric type folds. Bx site: indicates the biopsy site in panel A. Panel C: H&E stain; courtesy of Prof. Dr. Fritz Wrba and Dr. Ildiko Mesteri, Pathology Department, Medical University of Vienna.