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The Rapid Rise in Gastroesophageal Junction Tumors: Is Inflammation of the Gastric Cardia the Underwater Iceberg?

MICHAEL QUANTE,

II. Medizinische Klinik Klinikum rechts der Isar München, Germany

JULIAN A. ABRAMS, and

Department of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, New York

TIMOTHY C. WANG

Division of Digestive and Liver Diseases, Department of Medicine and Irving Cancer Research Center, Columbia University Medical Center, New York, New York

Over the last 40 years, there has been a rapid rise in the incidence of esophageal adenocarcinoma (EAC) as well as proximal gastric cardia adenocarcinoma (GCC, also known as junctional adenocarcinoma). Although most of the focus has been on EAC, which has been strongly linked to Barrett's esophagus (BE), GCCs arise in a contiguous location at the squamocolumnar junction (SCJ), and are often difficult to distinguish from EAC at a clinical or pathologic level. Furthermore, whereas gastroesophageal reflux and BE are clearly defined risk factors for EAC, most patients with EAC do not have a strong history of reflux, and EAC lesions show surrounding or associated specialized BE mucosa in fewer than half of cases. Recent publications have raised the question of whether EAC and GCC might possibly arise from the same origin and should therefore be described as one entity.^{1–4} Moreover, in the clinical setting, screening and surveillance of at-risk patients has been limited to individuals with BE with intestinal metaplasia (IM), and this strategy is unlikely to impact the overall incidence of EAC/GCC. It remains unclear as to whether any patients without reflux symptoms should be considered for screening. In addition, no efforts have been made to identify patients at risk for GCC, in part because risk factors and markers for GCC are poorly described.

In this issue of *Gastroenterology*, Robertson et al⁵ provide new and highly provocative insights into events occurring at the SCJ in asymptomatic, middle-aged individuals. They studied 51 volunteers (average age 45–46), roughly half of which had a small waist circumference (WC) and body mass index (median, 23.6 kg/m²), and half of whom had a large WC and body mass index (median, 30.5 kg/m²). The investigators used jumbo biopsies that included both squamous mucosa and oxyntic mucosa at the ends of each specimen, which allowed an assessment of the exact length of the cardiac mucosa. Few studies have used this approach to so precisely define the size of the cardiac mucosa. They also used elegant pH and manometric studies to analyze the lower esophageal sphincter (LES), both in terms of length and the leading edge of gastric acidity. Overall, the investigators found that patients with a large WC exhibited significant lengthening of the cardiac mucosa. Although

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Reprint requests: Address requests for reprints to: Timothy C. Wang, MD, Chief, Division of Digestive and Liver Diseases, Silberberg Professor of Medicine, Department of Medicine and Irving Cancer Research Center, Columbia University Medical Center, 1130 St. Nicholas Avenue, Room 925, New York, New York 10032-3802. tcw21@columbia.edu.

Conflicts of interest

The authors disclose no conflicts.

none of the patients showed classical acid reflux (by a drop in pH 5 cm above the LES), patients with a large WC showed a greater proximal extension of gastric acid within the LES, which was associated with shortening of the distal component of the LES. The increased gastric acid within the LES was attributed to the obesity and increased intra-abdominal pressure, and the investigators conclude that this undetected acid reflux led to damage to the SCJ (associated with glandular atypia) and expansion of adjacent cardiac glands. Although the study by Robertson et al⁵ was not designed to assess long-term cancer risk, these expanding cardiac glands, similar to the columnar-like epithelium (CLE) most commonly associated with EAC and GCC, may represent the undetected precursor lesion responsible for the rise in these proximal gastroesophageal cancers.

The authors discuss the expansion of the gastric cardia, and propose several potential explanations. Although some consideration is given to the possibility of “metaplasia of the most distal esophageal squamous epithelium,” we agree more strongly with the alternative explanation of “proximal extension of original cardiac mucosa.” Indeed, Norman Barrett himself initially assumed that BE resulted from proximal migration of stomach epithelium just below the gastroesophageal junction (ie, the gastric cardia),⁶ and the results of the present paper are more consistent with this concept. Over the past several decades, reflux-induced damage to the esophageal squamous epithelium was admittedly believed by many to lead to reprogramming or trans-differentiation of squamous epithelial cells. However, recent studies using murine models have convincingly shown that severe damage to the distal esophagus leads to migration of progenitor cells from the cardia into the esophagus. In a study by Wang et al,⁴ damage to the SCJ induced by Cre-mediated activation of diphtheria toxin A led to replacement of squamous epithelium by expanding columnar Krt7⁺ progenitor cells at the SJC. In a study by Quante et al,¹ in a transgenic interleukin (IL)-1b mouse model of chronic esophagitis progressing to BE and EAC, the origin of the BE-like lesions could be ascribed to Lgr5⁺ progenitor cells in the cardia through lineage tracing.¹ In this mouse model, a marked expansion of the gastric cardia was shown to occur in response to IL-1b-mediated inflammation in the squamous esophagus, leading to proximal migration of CLE (Figure 1). Indeed, at early time points, there were remarkable similarities between the murine cardia expansion in the L2-IL-1b mouse model and the changes seen in the human large WC group from the current study. Although the precise stem cells involved requires further confirmation, the studies are in agreement that damage to the distal esophagus initiates a wound repair response, with expansion and migration of columnar stem cells from the cardia to replace or push aside damaged squamous epithelium (Figure 1). Furthermore, the notion that metaplasia in the cardia can spread proximally has recently been confirmed in humans in the ProGERD study, where 20% of patients with gastroesophageal reflux with cardia IM were found to have BE within 2–5 years.⁷

Interestingly, in the current study of patients without reflux or *Helicobacter pylori*, 4 out of 62 patients (6.5%) showed IM within the cardia biopsies. Although BE is widely defined by the presence of specialized IM, the presence of goblet cells as a requirement for BE and as a risk factor for EAC has come under increasing scrutiny in recent years, and it is not clear what cancer risk IM in the cardia implies. Robertson et al⁵ discuss the fact that both classical IM (specialized BE) and expanded nonspecialized CLE within the cardia may be highly prevalent in asymptomatic populations that currently do not undergo screening or surveillance. In this regard, we would favor a model where stem cells from the cardia differentiate first into CLE, and then only later into IM, and that both should be viewed as risk factors for the development of junctional or esophageal cancer. In light of the ProGERD study findings,⁸ we believe that the differentiation of stem cells into specialized cell types, such as goblet cells, and the expansion in the esophagus may reflect more the duration of “disease” rather than necessarily a prerequisite for cancer progression, and can indeed be already seen in the cardia without the endoscopic evidence for BE in the esophagus.

The study by Robertson et al demonstrates nicely that a large WC/obesity can predispose to an expansion of the gastric cardia, and it now seems clear that obesity is a systemic inflammatory disease that can worsen localized inflammation by up-regulating numerous pro-inflammatory cytokines and chemokines (Figure 1), resulting in increased trafficking of myeloid cells.⁹ However, the increased inflammation observed in the cardia and SCJ in the setting of obesity could also be mediated by mechanical factors, resulting in an increased intra-abdominal pressure and thus increased acid exposure within the LES (Figure 1). In the current study, subjects with large WC had increased intragastric pressures and shortened LES lengths, and a decrease in LES pressure in and of itself (independent of acid exposure) might promote inflammation, cardiac lengthening, and proximal SCJ migration. Patients with BE have a very high prevalence of hiatal hernias, and perhaps a decrease in distal LES pressure is a precursor event to the development of a hiatal hernia. An additional possibility is that a decrease in LES pressure results in increased shear forces on the cardiac mucosa, in turn stimulating local inflammation. However, although obesity is likely an important factor, it remains to be answered whether obesity is the entire story then for the marked rise in BE and EAC. Two recent, population-based studies indicated that the incidence of EAC actually began to rise in the late 1960s, predating the rise in obesity by at least a decade,¹⁰ and estimated that obesity accounted for only 6.5% of the rise in EAC between 1973 and 2005.¹¹ Thus, these data suggest that obesity can exacerbate the rise in EAC, but may not be the primary cause.

Indeed, one of the more remarkable findings of the Robertson et al study was the presence of the reported “universal” inflammation with increases in both neutrophils and monocytic cells in all of the cardia biopsies examined (Figure 1), including those from patients with small WC. In addition, in this cohort of 51 patients, the other major risk factor for expansion of the gastric cardia was age. This actually raises the question as to whether “carditis” and an “expanded gastric cardia” might represent a normal aging process, as initially suggested by Chandrasoma.¹² Before the discovery of *H pylori*, chronic gastritis was also found to be nearly universal in older patients and misleadingly viewed as a normal aging process. Thus, one must view with some skepticism the notion that any chronic inflammatory state at the SCJ is likely to be “normal.” All of the patients in the current study were *H pylori* negative, and *H pylori* infection has a well-established inverse association with EAC.^{13,14} Although *H pylori* infection could also induce “carditis,” one wonders whether *H pylori* infection could in some way be protective against the carditis observed in this study, acting as a “suppressor” of cardia expansion at the SCJ (Figure 1). The decline in *H pylori* infection did in fact start a decade or more before the rise in BE. In addition, inflammation and IM of the distal esophagus are associated with alterations in the microbiome.¹⁵ However, at this point in time, one can only speculate as to whether changes in the microbiome of the upper gastrointestinal tract can be linked causally to the almost universal inflammation of the gastric cardia now observed in *H pylori*-negative, middle-aged patients.

Finally, multiple studies indicate an important role for bile acids as one component of gastroduodenal reflux that have been strongly linked to the development of BE and junctional cancers.^{1,16–19} Bile acids change the inflammatory microenvironment^{1,2} and potentially alter the microbiome. Thus, bile acid reflux could be another piece to the puzzle, which could help to explain the observed junctional inflammation (Figure 1). In the Robertson study, only a proximal extension of gastric acid was determined, and it remains to be determined whether obese patients might have a greater proximal extension of bile acid within the LES that induces damage and a tumorigenic microenvironment.

In summary, the elegant work by Robertson et al calls for increasing attention to chronic inflammation and expansion of the gastric cardia, which may represent the major precursor lesion for gastroesophageal junctional tumors. As a malignant precursor, specialized

Barrett's metaplasia of the esophagus may only represent the tip of the iceberg, and as pointed out in the current study,⁵ "carditis" may be much more frequent and constitute the bulk of the iceberg, underwater and potentially not seen. Classical reflux and classical IM of the esophagus do represent significant risk factors for EAC, but they may not be sufficiently sensitive to combat the disease. Further studies are needed to identify the importance of cardia inflammation and expansion as a precursor to cancer to develop more effective risk assessment strategies for screening and surveillance.

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References

1. Quante M, Bhagat G, Abrams JA, et al. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell*. 2012; 21:36–51. [PubMed: 22264787]
2. Quante M, Abrams JA, Lee Y, et al. Barrett esophagus: what a mouse model can teach us about human disease. *Cell Cycle*. 2012; 11:4328–4338. [PubMed: 23095673]
3. Xian W, Ho KY, Crum CP, et al. Cellular origin of Barrett's esophagus: controversy and therapeutic implications. *Gastroenterology*. 2012; 142:1424–1430. [PubMed: 22537611]
4. Wang X, Ouyang H, Yamamoto Y, et al. Residual embryonic cells as precursors of a Barrett's-like metaplasia. *Cell*. 2011; 145:1023–1035. [PubMed: 21703447]
5. Robertson EV, Derakhshan MH, Wirz AA, et al. Central obesity in asymptomatic volunteers is associated with increased intra-sphincteric acid reflux and lengthening of the cardiac mucosa. *Gastroenterology*. 2013; 145:730–739. [PubMed: 23796455]
6. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg*. 1950; 38:175–182. [PubMed: 14791960]
7. Leodolter A, Nocon M, Vieth M, et al. Progression of specialized intestinal metaplasia at the cardia to macroscopically evident Barrett's esophagus: an entity of concern in the ProGERD study. *Scand J Gastroenterol*. 2012; 47:1429–1435. [PubMed: 23110405]
8. Malfertheiner P, Nocon M, Vieth M, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care—the ProGERD study. *Aliment Pharmacol Ther*. 2012; 35:154–164. [PubMed: 22070159]
9. Ericksen RE, Rose S, Westphalen CB, et al. Obesity accelerates *Helicobacter felis*-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and TH17 response. *Gut*. 2013 May 31. Epub ahead of print.
10. Abrams JA, Sharaiha RZ, Gonsalves L, et al. Dating the rise of esophageal adenocarcinoma: analysis of Connecticut Tumor Registry data, 1940–2007. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:183–186. [PubMed: 21127287]
11. Kong CY, Nattinger KJ, Hayeck TJ, et al. The impact of obesity on the rise in esophageal adenocarcinoma incidence: estimates from a disease simulation model. *Cancer Epidemiol Biomarkers Prev*. 2011; 20
12. Chandrasoma P. Controversies of the cardiac mucosa and Barrett's oesophagus. *Histopathology*. 2005; 46:361–373. [PubMed: 15810947]
13. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res*. 1998; 58:588–590. [PubMed: 9485003]
14. Kamangar F, Dawsey SM, Blaser MJ, et al. Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. *J Natl Cancer Inst*. 2006; 98:1445–1452. [PubMed: 17047193]

15. Yang L, Lu X, Nossa CW, et al. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology*. 2009; 137:588–597. [PubMed: 19394334]
16. Kaur BS, Triadafilopoulos G. Acid- and bile-induced PGE(2) release and hyperproliferation in Barrett's esophagus are COX-2 and PKC-epsilon dependent. *Am J Physiol Gastrointest Liver Physiol*. 2002; 283:G327–G334. [PubMed: 12121879]
17. Kazumori H, Ishihara S, Rumi MA, et al. Bile acids directly augment caudal related homeobox gene Cdx2 expression in oesophageal keratinocytes in Barrett's epithelium. *Gut*. 2006; 55:16–25. [PubMed: 16118348]
18. Souza RF, Krishnan K, Spechler SJ. Acid, bile, and CDX: the ABCs of making Barrett's metaplasia. *Am J Physiol Gastrointest Liver Physiol*. 2008; 295:G211–G218. [PubMed: 18556417]
19. Dvorak K, Payne CM, Chavarria M, et al. Bile acids in combination with low pH induce oxidative stress and oxidative DNA damage: relevance to the pathogenesis of Barrett's oesophagus. *Gut*. 2006; 56:763–771. [PubMed: 17145738]

Figure 1.

In a proposed model of Barrett's esophagus (BE), the proximal extension of original cardiac mucosa originates metaplasia in the esophagus. In obese patients, accelerated influx of immune cells and expression of cytokines, as well as an increased intra-abdominal pressure with an increased exposure of bile and gastric acid to the lower esophageal sphincter (LES) likely results in an altered microenvironment at the squamocolumnar junction (SCJ) that induce a lengthening of the cardiac mucosa through an expansion of adjacent cardiac glands.