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Cardiac Metaplasia: Follow, Treat or Ignore?

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Chronic inflammation can result in metaplasia, the process in which one type of tissue replaces another.[1] Presumably, metaplastic tissue develops and persists because it is better able to resist injury from the underlying condition causing the chronic inflammation than the native tissue. When chronic gastroesophageal reflux disease (GERD) inflames esophageal squamous mucosa and induces its replacement by an intestinal-type columnar mucosa with goblet cells, there is broad agreement that this is a metaplastic condition called Barrett's esophagus.[2] In contrast, there is international disagreement regarding whether a distal esophagus lined by cardiac mucosa, which also has intestinal features but lacks goblet cells, represents a metaplasia that qualifies for a diagnosis of Barrett's esophagus. To understand why this issue is so controversial requires considerable explanation.

What is Cardiac Mucosa and why is it Controversial?

Traditionally, cardiac mucosa has been considered one of three mucosal types normally found in the stomach.[3] The oxyntic mucosa (also called fundic mucosa) of the gastric body and fundus has glands harboring acid-secreting parietal cells, and chief cells that produce digestive enzymes. The pyloric gland mucosa of the gastric antrum is comprised of mucus-secreting glands, which also contain numerous endocrine cells that secrete the hormone gastrin. Cardiac mucosa (also called junctional mucosa), which has mucus-secreting glands exclusively, has been assumed to line the normal gastric cardia, the most proximal portion of the stomach. Cardiac mucosa can be subcategorized as oxyntocardiac if its mucus glands also contain some parietal cells. Oxyntic, pyloric and cardiac mucosae all have a surface epithelium comprised of tall, columnar, mucus-secreting foveolar cells. Although the depth and structure of the gastric pits lined by these foveolar cells differ somewhat among oxyntic, pyloric and cardiac mucosae, these mucosal types are distinguished from one another primarily by their glands, not by their surface epithelium. Hence, some pathologists object to the term "cardiac epithelium" (since it is the underlying mucus glands that identify the mucosa as cardiac), and prefer to call the epithelial component of cardiac mucosa "non-goblet columnar epithelium" to distinguish it from the goblet-containing columnar epithelium of typical Barrett's metaplasia (see below).[4] Over the past two decades, data have accumulated to suggest that cardiac mucosa might not be a normal gastric lining, but rather a

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GERD-induced metaplasia of the esophagus, even in what appears grossly to be the proximal stomach.

Some of the confusion about the nature of cardiac mucosa stems from imprecision in landmarks used to identify the anatomic gastric cardia, which is far easier to describe conceptually than practically. Conceptually, the gastric cardia is the most proximal part of stomach that starts where the esophagus ends. Practically, there is no anatomic structure that clearly delimits the “end” of the esophagus. Endoscopists in Western countries identify the end of the esophagus by the location of the proximal extent of gastric rugal folds. In some Asian countries, endoscopists use the distal extent of the esophageal palisade vessels (endoscopically-visible, fine, longitudinally-oriented blood vessels in the lamina propria of the distal esophagus) as their landmark for the end of the esophagus.[6] Both of these landmarks have been chosen arbitrarily, and neither provides a crisp or immutable border. The proximal extent of gastric folds can vary from moment to moment depending on the degree of esophageal and gastric distention, and the distal border of the palisade vessels forms a jagged edge that can be obscured by inflammation. As poorly defined as is the proximal border of the gastric cardia, there is no anatomic landmark for its distal extent.

Traditional teaching holds that cardiac mucosa normally lines several centimeters of the proximal stomach.[7] In 1961, an Australian surgeon named John Hayward contended (without citing evidence) that cardiac mucosa also normally lines up to 2 cm of the distal esophagus, where it functions as a buffer zone to prevent the damage that might result if the acid-sensitive squamous mucosa of the esophagus joined directly with the acid-secreting oxyntic mucosa of the stomach.[8] Without precise landmarks for the gastro-esophageal junction (GEJ), however, it is not possible to ascertain whether short segments of cardiac mucosa in this region line the esophagus or the stomach.

In 1997, Parakrama Chandrasoma, a pathologist working with a group of esophageal surgeons led by Tom DeMeester at the University of Southern California, proposed the novel concept that cardiac mucosa is not a normal gastric lining, but rather is a metaplastic *esophageal* lining acquired as a result of GERD.[9] This proposal was based on his observations that autopsy examinations of the GEJ in patients without GERD often revealed esophageal squamous mucosa directly abutting gastric oxyntic mucosa with no intervening cardiac mucosa, and that other such patients had segments of cardiac mucosa extending only millimeters in length and virtually always showing inflammation. He hypothesized that squamous mucosa normally joins oxyntic mucosa at the GEJ but, in the setting of GERD with chronic reflux esophagitis, cardiac mucosa develops through a metaplastic process and, with ongoing GERD, cardiac mucosa later evolves into the intestinal metaplasia of Barrett’s esophagus.

Chandrasoma extended his hypothesis in a report describing 10 esophago-gastrectomy specimens that had cardiac and oxyntocardiac mucosae lining rugal folds in what appeared to be the proximal stomach, except that the underlying submucosa revealed *esophageal* submucosal glands.[10] This led him to propose that the endoscopic criterion for the GEJ (the proximal extent of gastric folds) is not valid, and that rugal folds lined by cardiac mucosa are not in the stomach at all, but rather in a dilated segment of reflux-damaged, distal esophagus

that is mistaken for the stomach. Finally, Chandrasoma proposed that, if there is a segment of columnar mucosa comprising cardiac, oxyntocardiac or intestinal metaplasia interposed between esophageal squamous mucosa proximally and gastric oxyntic mucosa distally, then this “squamo-oxyntic gap” region represents a columnar-lined esophagus whose length is an index of GERD severity.[11]

Chandrasoma’s hypothesis on the nature of cardiac mucosa remain highly controversial. In attempts to elucidate whether cardiac mucosa is a normal, congenital structure or an acquired metaplasia as Chandrasoma contends, investigators have conducted autopsy studies on the histology of the GEJ in children without GERD. Unfortunately, such studies have yielded contradictory results (finding cardiac mucosa at the GEJ with frequencies ranging from 0 to 100%), and the reason for these major discrepancies among studies is not clear.[12,13] Nevertheless, a number of observations do provide some support for Chandrasoma’s proposals. For example, esophagectomy with gastric pull-up reconstruction often results in severe reflux esophagitis in the esophageal remnant, which frequently acquires a columnar lining with cardiac mucosa appearing first, followed years later by intestinal metaplasia.[14] This is strong evidence that cardiac mucosa can be metaplastic, and the precursor of intestinal metaplasia. In addition, cardiac mucosa can express intestinal-type acidic mucins as well as molecular markers of intestinal differentiation such as villin and CDX2,[4,15] and can exhibit DNA content abnormalities similar to those of intestinal metaplasia with goblet cells.[16]

Recent reports from Kenneth McColl’s group in Glasgow also strengthen the contention that cardiac mucosa is a GERD-induced metaplasia. These investigators studied 51 healthy volunteers who had normal esophageal acid exposure by conventional pH monitoring in which the pH electrode was positioned 5 cm above the lower esophageal sphincter (LES).[17] Using pH electrodes positioned *within* the LES, however, the investigators found that their 27 subjects with large waists had more proximal extension of gastric acid within the LES (resulting in protracted acid exposure of the distal-most, squamous-lined esophagus) than the 24 small-waisted subjects. The subjects with central obesity also had a significantly greater length of cardiac mucosa than the subjects with small waists (2.5 *vs.* 1.8 mm), and all of the cardiac mucosa identified was inflamed, irrespective of the subject’s waist circumference. Another study of these healthy individuals showed that those with hiatal hernias had increased intrasphincteric reflux that was associated with lengthening of the cardiac mucosa.[18] Yet another study compared biopsies from the healthy volunteers with those from 15 patients with long-segment Barrett’s esophagus.[19] The intensity of inflammation in cardiac mucosa was similar to that in Barrett’s metaplasia, and the cardiac mucosa of the healthy volunteers exhibited an immunohistochemical staining pattern almost identical to that of cardiac mucosa in the Barrett’s patients.

The aforementioned studies support but do not prove the notion that cardiac mucosa at the GEJ is always metaplastic. These studies do show that cardiac mucosa is present in a very narrow strip (usually extending no more than 3 mm) at the GEJ in the large majority of apparently normal individuals. However, this observation does not establish that cardiac mucosa is a normal structure. Autopsy studies of young men who died of trauma have shown that more than 75% have evidence of atherosclerosis but, despite its great frequency,

atherosclerosis generally is not considered a normal condition.[20] The fact that cardiac mucosa virtually always shows signs of chronic inflammation also argues against it being a "normal" structure.

The Goblet Cell in Barrett's Esophagus

To non-pathologists perusing biopsy specimens under the microscope, the goblet cell, with its distinctive, goblet-shaped apical mucin droplet, is perhaps the most readily recognized histologic feature of Barrett's metaplasia. Since goblet cells normally are intestinal cells, their presence in biopsies of the esophagus or stomach immediately identifies a pathological condition. Although, as mentioned above, cardiac mucosa expresses molecular markers of intestinalization, the term "intestinal metaplasia" generally has been used only to describe a mucosa that contains goblet cells.

In the United States, an esophageal biopsy demonstrating intestinal metaplasia with goblet cells is required to confirm an endoscopic diagnosis of Barrett's esophagus.[21] However, this requirement creates problems related to both underdiagnosis and overdiagnosis of the condition. There is often a patchy distribution of goblet cells in the columnar-lined esophagus, and one study of 125 patients with such an esophagus concluded that at least 8 random esophageal biopsies were required to find intestinal metaplasia (i.e. goblet cells) reliably.[22] Since endoscopists generally take far fewer biopsies of the columnar-lined esophagus than recommended,[23] it is likely that Barrett's esophagus often is underdiagnosed. On the other hand, foveolar cells occasionally can become so distended with mucin that they are mistaken for goblet cells (so-called "pseudogoblet cells"), resulting in overdiagnosis of Barrett's esophagus.24 Thus, the goblet cell is an imperfect marker for intestinal metaplasia.

Although it has been assumed that the primary function of goblet cells is to secrete mucus, they also deliver luminal antigens to CD103+ dendritic cells in the small intestine. The latter observation suggests that goblet cells might have a role in maintaining immune tolerance to commensal bacteria and food in the gut.[25] Whatever their function, goblet cells are highly differentiated and, as such, are unlikely candidates for the cells of origin of esophageal adenocarcinoma. Nevertheless, the goblet cell is considered a marker for the malignant predisposition of Barrett's metaplasia, which is why American GI societies require goblet cells for a diagnosis of Barrett's esophagus.

Cardiac Mucosa as a Diagnostic Criterion for Barrett's Esophagus

There is no universally accepted definition of Barrett's esophagus, and the condition we now call Barrett's esophagus bears little resemblance to what Norman Barrett first described in 1950. Barrett did not mention intestinal metaplasia in his report on the columnar-lined viscus we now identify as Barrett's esophagus, and he originally contended that the viscus was not esophagus at all but rather a tubular segment of stomach that had been tethered within the chest by a congenitally short esophagus.[26] Definitions of the disorder have evolved considerably over the years as physicians acquired a better understanding of the nature of the columnar-lined esophagus and of how it predisposes to esophageal adenocarcinoma. There

is general agreement that Barrett's esophagus is the condition in which a metaplastic columnar mucosa replaces the stratified squamous mucosa of the distal esophagus, but there is considerable disagreement regarding the extent and type of columnar metaplasia required to make the diagnosis.

In 1976, a report by Paull *et al.* described 11 patients with Barrett's esophagus who had esophageal biopsies taken using manometric guidance to ensure that the specimens came from esophagus proximal to the LES.[27] Patients were found to have three types of columnar epithelia lining their Barrett's esophagus: 1) specialized columnar epithelium (now called "specialized intestinal metaplasia" or simply "intestinal metaplasia") with prominent goblet cells, 2) junctional (now called cardiac or non-goblet columnar) epithelium comprised exclusively of mucus-secreting cells and, 3) atrophic gastric fundic-type epithelium (now called oxyntocardiac) with mucus-secreting cells and some parietal cells. Early reports on adenocarcinomas developing in Barrett's esophagus almost invariably described the non-malignant columnar epithelium surrounding the tumors as showing intestinal metaplasia with goblet cells.[28] By the 1980's, intestinal metaplasia was widely regarded as the most common and distinctive type of Barrett's metaplasia, and the one associated with cancer development, By the 1990s, the identification of goblet cells in the esophagus had become a *sine qua non* for the diagnosis of Barrett's esophagus in the United States and many other countries.[28]

As discussed above, cardiac mucosa has intestinal features despite its lack of goblet cells and, since 1997, data have accumulated to suggest that cardiac mucosa is both metaplastic itself and the precursor of intestinal metaplasia. In 2006, the British Society of Gastroenterology (BSG) defined Barrett's esophagus as one with an endoscopically-apparent area of columnar epithelium extending above the GEJ, and they departed from American guidelines by stating specifically that intestinal metaplasia was *not* a requirement for the diagnosis.[29] The BSG accepted an esophagus lined by cardiac mucosa as a Barrett's esophagus because British pathologists believed that, "If a sufficient number of biopsies are taken over an adequate period of time, intestinal metaplasia can usually be demonstrated (in the majority of these patients)." Thus, the BSG's modification of diagnostic criteria for Barrett's esophagus was not based primarily on concern regarding the metaplastic nature or malignant potential of cardiac mucosa itself, but rather on concern that intestinal metaplasia could be missed due to biopsy sampling error in patients found to have only cardiac mucosa lining the distal esophagus. In revised guidelines on the diagnosis of Barrett's esophagus published in 2014, the BSG retained its position that intestinal metaplasia was not required for the diagnosis of Barrett's esophagus, but added the stipulation that there must be a segment of endoscopically-visible columnar lining extending at least 1 cm above the GEJ to establish the diagnosis.[30]

Cardiac Mucosa as a Risk Factor for Esophageal Adenocarcinoma

Authorities continue to disagree on the issue of proper diagnostic criteria for Barrett's esophagus. Since the criteria have evolved considerably over the years, and the definition originally proposed by Barrett himself is no longer accepted, debates regarding diagnostic criteria for this disorder necessarily involve arbitrary features. Nevertheless, these debates

often revolve around one critical issue: Does columnar epithelium in the esophagus predispose to cancer? If so, then it is a medical condition that warrants attention. If not, then it is an anatomic curiosity of little importance. Most of what is known about cancer risk in Barrett's esophagus is based on studies that included patients with intestinal metaplasia either primarily or exclusively. For patients with non-dysplastic intestinal metaplasia in Barrett's esophagus, the risk of developing esophageal adenocarcinoma presently is estimated at approximately 0.1% to 0.3% per year.[2] The cancer risk imposed by cardiac metaplasia in the esophagus is far less clear.

Some studies suggest that cardiac mucosa in the esophagus poses an important cancer risk. For example, a study of 141 patients who had endoscopic mucosal resection (EMR) of small esophageal adenocarcinomas found that 71% had cardiac mucosa, not intestinal metaplasia, adjacent to the cancer.[31] In addition, intestinal metaplasia was not observed in any area of the EMR specimen in 57% of the cases. This led the study authors to question conventional dogma that esophageal adenocarcinoma is usually accompanied and preceded by intestinal metaplasia, and to suggest that intestinal metaplasia with goblet cells should not be a necessary diagnostic criterion for Barrett's esophagus.

One retrospective study of 688 patients in one hospital who had endoscopic biopsy specimens taken from the distal esophagus (379 with intestinal metaplasia, 309 with glandular mucosa without intestinal metaplasia) found no significant difference in the rate of esophageal adenocarcinoma development between patients with and without goblet cells in their esophageal columnar epithelium (4.5% vs. 3.6% rate of cancer development, respectively) during a median follow-up interval of 12 years.[32] Another retrospective study of 1,751 patients with columnar-lined esophagus on endoscopy found that 66% had intestinal metaplasia and 34% did not.[33] Follow-up was available for a group of 612 patients with intestinal metaplasia and 322 patients without it and, during a median follow-up of 3.5 years, there was no significant difference in the rate of adenocarcinoma development between those groups. Within 5 years, furthermore, intestinal metaplasia was found in 55% of patients without it at index endoscopy, increasing to 91% by 10 years. The authors concluded that intestinal metaplasia eventually will be demonstrated in patients with columnar-lined esophagus if sufficient biopsies are taken over time, and that the decision to offer surveillance should not be based upon the presence or absence of intestinal metaplasia at index endoscopy since the risk of adenocarcinoma is similar in both groups. In both of these studies, however, it appears that an insufficient number of biopsies was taken to exclude intestinal metaplasia at the index endoscopies.

In contrast to the studies just described above, several studies suggest that the cancer risk imposed by cardiac mucosa is vanishingly small, and that intestinal metaplasia is not always found on follow-up. In a study from a surgical referral center of 214 patients with a columnar-lined esophagus who had 4-quadrant biopsies take at 1 to 2 cm intervals, the investigators found dysplasia or adenocarcinoma in 55 of 187 patients with intestinal metaplasia in those biopsies, but in none of 27 patients whose biopsies showed only cardiac mucosa.[34] A study of 8,522 patients with columnar-lined esophagus identified in the Northern Ireland Barrett's Esophagus Register and followed for a mean of 7 years found a significantly higher rate of esophageal cancer development in patients with intestinal

metaplasia in their index biopsies than in those without (0.38% per year vs 0.07% per year; hazard ratio=3.54, 95% CI=2.09 to 6.00, P < .001).[35] Investigators at the University of Chicago identified 637 patients who had esophageal biopsies taken for suspicion of Barrett's esophagus, and found that 258 had intestinal metaplasia with goblet cells while 379 did not.[36] Among the 379 patients without goblet cells, 118 had follow-up endoscopic examinations and, during a mean period of 5.8 years, goblet cells were eventually identified in only 12%. Furthermore, no patient without goblet cells on index endoscopy developed dysplasia or cancer. The investigators concluded that adopting the BSG guideline to drop the diagnostic requirement for goblet cells would have increased the frequency of diagnosis of Barrett's esophagus by 147%, and would have included many patients who appear to have little risk for cancer development. Another study of 107 patients suspected of having Barrett's esophagus, but with no intestinal metaplasia seen in esophageal biopsies, found intestinal metaplasia in follow-up biopsies performed within 2 years in only 29%, and none showed evidence of dysplasia or cancer.[37]

The reasons for the discrepancies among studies on the risk of cancer imposed by cardiac mucosa are not entirely clear, but a number of potentially confounding factors should be considered when reviewing these data. First, as discussed above, cardiac mucosa appears to be present at the GEJ in most healthy adults, but studies on cardiac mucosa and cancer risk have focused primarily on patients with GERD symptoms who had an endoscopy showing a columnar-lined esophagus. Thus, those studies probably are not representative of the large majority of individuals with cardiac mucosa at the GEJ. In studies that have focused on cancer risk in patients with cardiac mucosa in a columnar-lined esophagus, furthermore, the number of biopsy specimens often was inadequate to exclude any accompanying intestinal metaplasia. Thus, inadequate biopsy sampling undoubtedly resulted in some patients with intestinal metaplasia being misclassified as intestinal metaplasia-negative. A number of studies had relatively small numbers of patients with cardiac metaplasia followed for short durations, features that also might bias estimates of cancer risk. Despite all the contradictory and unreliable data, however, the bulk of evidence suggests that the cancer risk imposed by cardiac mucosa alone (without intestinal metaplasia) is minimal.

Because of uncertainties regarding the importance of cardiac metaplasia, the authors of the American Gastroenterological Association's position statement on the management of Barrett's esophagus made a distinction between their conceptual definition of Barrett's esophagus and its diagnostic criteria.[38,39] They defined Barrett's esophagus conceptually as "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus," and concluded that, "Presently, intestinal metaplasia [with goblet cells] is required for the diagnosis of Barrett's esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy." I feel that statement remains valid. This conceptual definition of Barrett's esophagus as a condition that predisposes to cancer will not change if future studies verify the malignant potential of cardiac mucosa, but the diagnostic criteria for the condition might require alteration.

Key Findings, Future Unmet Needs, and Implications for the Clinician

It is not clear that cardiac mucosa is ever a normal gastric lining. There is compelling evidence that cardiac mucosa develops as a GERD-induced, squamous-to-columnar metaplasia in some, if not all cases. Cardiac mucosa has intestinal features, and appears to be the precursor of intestinal metaplasia with goblet cells. In apparently normal individuals, cardiac mucosa typically is present in a narrow band, less than 3 mm in extent, on the columnar side of the squamo-columnar junction at the end of the esophagus. A greater extent of cardiac mucosa can be found in GERD patients, and the magnitude of that extent appears to be an index of GERD severity. The observation that esophageal glands are present in the submucosa of rugal folds that are lined by cardiac mucosa in what appears to be the proximal stomach suggests that the proximal extent of rugal folds might not be a valid landmark for the GEJ. Finally, the risk of adenocarcinoma imposed by cardiac mucosa is not clear.

The most pressing future unmet need is for well designed, prospective studies of patients with a cardiac mucosa-lined esophagus to assess their cancer risk. Such studies will require standardized, extensive biopsy protocols to ensure that patients have a sufficient number of biopsies taken to detect goblet cells on their first and subsequent endoscopies, and will require large numbers of patients followed for protracted periods.

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Implications for the Clinician

- Biopsies should not be taken from a normal-appearing squamo-columnar junction (Z-line) because they are likely to reveal cardiac mucosa, a finding that has no clear clinical implications, but has the potential to create undo patient anxiety and result in unwarranted procedures.
- For patients found to have only cardiac metaplasia without goblet cell intestinal metaplasia in a columnar-lined esophagus, the presence of accompanying intestinal metaplasia is not reliably excluded unless at least 8 biopsies have been obtained.
- A diagnosis of Barrett's esophagus should not be made in patients with only cardiac mucosa in a columnar-lined esophagus (although BSG guidelines say otherwise).
- Given the limitations and heterogeneity of available studies on cancer risk for patients who have only cardiac metaplasia in the columnar-lined esophagus, no meaningful, blanket recommendation for surveillance can be provided at this time.