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Review

Gastric cardia cancer and precursor lesions- current dilemmas

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SUMMARY

Over the last two decades a marked increase in the incidence of adenocarcinoma of the gastroesophageal junction has been observed. This carcinoma can develop, either from short segment Barrett's esophagus or metaplastic gastric epithelium in the cardia. Much confusion exists regarding the malignant potential of such short segments of intestinal metaplasia, at or above the esophagogastric junction. Furthermore, it is currently unclear whether intestinal metaplasia at the esophagogastric junction and in the distal esophagus, represent a continuum of the same underlying disease process, i.e., gastroesophageal reflux, or constitute different entities with a different pathogenesis. Such a difference may not be crucial since all patients with cancer would undergo surgical procedure, but the identification of precursor lesions is merited since different therapeutic and surveillance protocol can be established. Biopsies below the Z line might show specialized epithelium in some patients and the question is whether this is another form of short segment Barrett's esophagus or whether it is related to a generalized atrophic process of the stomach. Epidemiological data and classic parameters for the diagnosis of gastroesophageal reflux disease do not currently support a causal role of gastroesophageal reflux in the pathogenesis of specialized intestinal metaplasia of the gastric cardia. Results from recent studies still leave us with a dilemma concerning the role of reflux disease and Helicobacter pylori infection in the development of carditis and consecutive intestinal metaplasia. It appears that such discrepancies often originate from different biopsy sampling protocols. At present, there are no accepted criteria concerning the position of gastric cardia. Anatomic and histological landmarks do not always coincide. A promising tool for future investigation may be the different expression of cytokeratins in metaplastic epithelium arising from the esophageal, as opposed to the gastric mucosa. This article reviews the results of the recent studies and presents dilemmas relating to the burning issue of gastric cardia cancer.

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INTRODUCTION

The incidence of adenocarcinoma of the gastroesophageal junction is on the increase.[1] For the last three decades the death rates for these tumors have risen from 1.5 to 3/100 000. Time trends of these carcinomas differ from those in the distal stomach and resemble those of the distal esophagus.[2]

Gastric cardia and carditis have drawn much of the attention, resulting in a number of published articles. We have been focusing on the intestinal metaplasia of the esophagus for many years. More recently, we have also begun to realize the importance of the most proximal part of the stomach - cardia, where intestinal metaplasia may also be found.[3-5] This is certainly one of the most intriguing topics in gastroenterology for gastroenterologists, pathologists, as well as surgeons, particularly in light of the rising incidence of adenocarcinoma of the gastroesophageal junction (GEJ).[1,6] It is important to understand this region better because, in addition to the increasing incidence of adenocarcinoma of the esophagus, adenocarcinoma of the cardia is increasing in parallel fashion.[7-8]

EPIDEMIOLOGY (DEMOGRAPHICS)

Adenocarcinomas of the esophagus and gastric car-

dia share similar epidemiological and pathological features. Both are more common in white males. The ratio of males to females appears to be a little higher for esophageal than for cardia adenocarcinoma, but the difference is not of statistical value. The age of diagnosis is similar (60-65 years), with a tendency for cardia adenocarcinoma to be diagnosed at a later age. Some authors have reported differences in risk factors, between patients with cardiac and esophageal adenocarcinoma. There may be a stronger history of smoking and alcohol consumption in patients with adenocarcinoma of the cardia.[9]

Morphology: cardia or short segment of Barrett's esophagus?

Definitions:

- The gastroesophageal junction has been arbitrarily defined by endoscopists as the proximal margin of the gastric folds.[10]
- The squamo-columnar junction (SCJ) is a Z-shaped, sharp line where squamous epithelium of the esophagus and the columnar epithelium of the stomach adjoin. Endoscopically, it is a line where the salmon pink color of the esophageal mucosa converts to the red color of the stomach mucosa.
- Cardiac-type mucosa is characterized by unequivocal PAS positive mucous secreting glands arranged in a lobular configuration.[11,12]
- The "transition zone" is the zone composed of a mixture of mucous glands and parietal cells. The length of "transition zone" is the distance between the most distal aspect of the cardiac-type mucosa to the point at which the mucosa is composed entirely of fundic type glands.[12]
- The traditional definition of Barrett's esophagus is: "At least 3 cm of circumferential columnar lining in the distal esophagus with histologic proof of specialized intestinal metaplasia (often referred to as long segment or classic Barrett's esophagus)".[13] A more recent one states: "Barrett's esophagus is a replacement of the squamous mucosa of the lower esophagus by glandular mucosa as a consequence of gastroesophageal reflux disease accompanied by intestinal metaplasia".[14]
- Short segment Barrett's esophagus are endoscopically visible tongues of columnar epithelium in the distal esophagus, less than 3 cm in length with histologic proof of specialized intestinal metaplasia.[15]

A purely endoscopic differentiation of these conditions is not possible. Rather, a clear description of the presence and length of a columnar lining of the distal esophagus on endoscopy, a careful histologic assessment of biopsies and documentation of the biopsy site, i.e., above or below the esophagogastric junction, are essential.

Gastric cardia

Normally, the mucosa of the cardia is composed of mucus-secreting glands[11]. In two recent articles based on prospective and retrospective autopsy findings[12,16], it was hypothesized that cardiac mucosa actually does not exist as a native structure, but rather arises as a metaplastic phenomenon in the distal esophagus secondary to gastroesophageal reflux. These authors noted that there are no uniformly accepted criteria by which gastroesophageal junction (GEJ) can be recognized, even when using autopsy or resection material. Therefore, Chandrasoma et al. in their studies did not specify the anatomical relationship between the various types of columnar mucosa and the GEJ. But, without defining the GEJ, the significance of the various types of mucosa existing in this region cannot be recognized. Furthermore, only by defining the GEJ can one possibly know whether or not gastric cardia exists.

However, other authors have noted that gastric cardia does exist. In a recent, very well designed study, on a series of 30 pediatric autopsies from patients aged 18 years or less with no known history of GERD or Barrett's esophagus, the Z-line (squamocolumnar junction) and its relationship to the GEJ were meticulously studied.[17] In this study, GEJ was defined as the site of the most proximal margin of the gastric folds. Cardiac-type mucosa was defined by the "unequivocal presence of PAS-positive mucus glands arranged in a lobular configuration". Cardiac mucosa was found to be present at birth and only 1-4 mm in length. Also, it was always found to be present on the gastric side of GEJ. It increases slightly with ageing, but the factors responsible are unknown. The length of the cardiac-type epithelium was taken to be the distance between the most distal portion of squamous mucosa and the site where the most proximal parietal cell was identified. Distance between the most distal aspect of the cardiac–type epithelium and mucosa composed of entirely fundic(oxyntic)-type glands was called the "transition zone". This transition zone was most often noted as a mixture of both type of glands (53%) or was abrupt (37%).

So it is to be emphasized that gastroesophageal junction (GEJ) and squamocolumnar junction (SCJ) may not

coincide in the normal stomach and as was stated by Spechler[18], "when the SCJ is located proximal to the GEJ, there is a self-evident columnar-lined segment of the esophagus". But in histological terms, the cardiac type of epithelium does exist and it starts at the SCJ, extending a variable but rather short distance. In anatomical terms, the cardiac type of epithelium usually belongs to the stomach, but it can also belong to the esophagus as well.

Short segment Barrett's esophagus vs. cardia

Barrett's esophagus is an acquired condition in which squamous epithelium of the distal esophagus is replaced by metaplastic columnar epithelium. It is a specific protective mechanism that can occur at any stage of the reflux disease.[13] Diagnosis of Barrett's esophagus is quite obvious when there is a long segment of pink mucosa in the esophagus. Some years ago[19], it became clear that a short segment of Barrett's esophagus (SSBE), i.e. metaplastic epithelium less than 3 cm in length, could be found in about 20% of patients without an endoscopically apparent "traditional" Barrett's esophagus.[3,4,20] According to Pereira et al.[21], there are two endoscopic features that are indications of short segment Barrett's esophagus: "a straight and regular Z line displaced upwards in relation to the gastro-esophageal junction by less than 3 cm (circumferential type); and an irregular Z line, with eccentric tongues of red mucosa extending above this junction (digitated type)". However, it can be argued, referring to both groups with circumferential and digitated type of SSBE, that biopsy specimens were actually taken from the gastric cardia. The authors conclude that specialized intestinal metaplasia is a consequence of gastro-esophageal reflux and they relied on symptom cluster, but not on objective measurements like histological verification of esophagitis. It is also not clearly stated at which distance from the SJC biopsy specimens were taken and which type of epithelium was found in these biopsy specimens. Most likely it was cardiac-type epithelium.

It was suggested by Haggitt et al.[22] that normally, in the distal 2 cm of the esophagus "only fundic or cardiac type of epithelium may occur without the presence of intestinal-type Barrett's esophagus". This was confirmed later by Weston et al.[23] who were frequently unable to find goblet cells in biopsy specimens of patients with suspected short segment compared with long segment Barrett's esophagus.

It is obvious from these studies that often, when short segment of Barrett's esophagus is suspected, histology examination can actually reveal intestinal metaplasia of the cardia-type of epithelium and vice versa. So, it is important in the evaluation of the histopathological changes in the gastric cardia, to measure both distances: a) front teeth-GEJ and b) front teeth-SCJ. This would provide information on the exact anatomic position of the SCJ and cardia. When the regular shaped SCJ is located proximal to the GEJ, there is a columnar-lined esophagus and short segment of Barrett's esophagus can be excluded. To ensure that biopsy specimens contain cardia mucosa, but not short segments of Barrett's esophagus, it is most convenient to take biopsy, with one biopsy cup positioned on the esophageal and the other one on the gastric side of the SCJ.

Inflammation and intestinal metaplasia in the gastric cardia

Occasionally, biopsy specimens from the cardia show chronic and sometimes acute inflammation, a condition termed carditis.[24,25] However, the causes of inflammation in cardia remain obscure.

The role of Helicobacter pylori infection

The importance of inflammatory process secondary to the Helicobacter pylori infection in other parts of the stomach is very well understood.[26] A long-term inflammatory process may, in some patients, proceed to the intestinal metaplasia of the involved epithelium.[27-29] Histologically and functionally, antrum and cardia share similar epithelium[11] with mucus secreting cells and similar local pH that determines the growth behavior of Helicobacter pylori[30,31] So it is not unreasonable to believe that inflammatory changes on those sites can have similar consequences regarding Helicobacter pylori infection.

There are investigators who find cardia frequently involved as a part of pangastritis related to Helicobacter pylori.[32,33] In the study of Genta et al., Helicobacter pylori were detected in the cardia in 40 out of 42 patients (95%) with Helicobacter pylori infection elsewhere in the stomach. Furthermore, the intensity of the chronic active gastritis was similar in the antrum and cardia, although the relationship with GERD was not specifically evaluated in this study. Goldblum et al. also found Helicobacter pylori present in a high proportion (94%) of patients with carditis, although the organism was identified only on Giemsa stain. Similar to Genta, these patients had inflammation in other parts of the stomach, suggesting a strong association between Helicobacter pylori infection and carditis. In this study, the intensity of inflammation and the degree of Helicobacter pylori colonization were similar to elsewhere in the stomach, which differs from previous findings by Morales et al.[4]

Goldblum et al.[32] found intestinal metaplasia more prevalent in the control group than in the GERD group (22% vs. 3%), making it clear that intestinal metaplasia of the cardiac mucosa has a different origin, most probably associated with Helicobacter pylori infection (88%). In the study of Hackelsberger et al.,[5] intestinal metaplasia was present in 13.4% and it was significantly associated with older age, Helicobacter pylori status and gastric intestinal metaplasia. Similar results were reported earlier by Morales et al.[4] and Trudgill[20] who found intestinal metaplasia in 23% and 18% respectively, of the patients without endoscopically apparent Barrett's esophagus. The main conclusion to be drawn, based on the results of these studies, is that cardiac IM is not related to GERD and the consecutive presence of Barrett's esophagus.

The role of reflux disease

On the other hand, some investigators believe that carditis and subsequently intestinal metaplasia of the cardiac mucosa are consequences of repeated injury of the cardiac epithelium by gastric and duodenal content, with duodenal components being the crucial agent.[13,25,34] The reason why the process is limited to the cardia in some patients while in others it involves the esophagus, is due to the competence of the lower esophageal sphincter.[34,35] But it is controversial that the authors refer to the inflammatory changes in this part of the stomach as carditis, since, as aforementioned, the same group of investigators found cardia not existing at birth.[16,25] Oberg et al.[25] found IM in 12% of the patients without GERD and it was not associated with IM elsewhere in the stomach or Helicobacter pylori infection, while Hirota et al.[36] found intestinal metaplasia in the cardia in only 5.3% of the patients without endoscopically apparent BE (Table 1).

There are several reasons for such differences in the prevalence of intestinal metaplasia, between these studies. One of them is certainly the aforementioned problem of identifying GEJ and its relationship to the SCJ and biopsy sampling. Taking biopsies distant to 4 mm circular region around normal appearing SCJ may reveal a transitional zone with parietal cell present, which share properties of both cardiac and fundic mucosa. If we assume that inflammation in cardia is part of gastritis according to the Sydney system,[37,38] in case of antrum predominant gastritis, with corpus mucosa spared from inflammatory process, obtaining the specimens distant to 5 mm of the SCJ, could reveal normal histology, although there is carditis present.

Detection of intestinal metaplasia also depends on the number of biopsy specimens taken, since intestinal metaplasia is usually patchy, and can easily be missed[39] (Table 2).

Intestinal metaplasia and gastric cardia cancer

Intestinal metaplasia was found in several studies in the peritumorous mucosa of the gastric cardia tumors, although, it was not always clear whether it has its origin in the esophagus or proximal stomach.[23,40,42] Thus, it is believed that intestinal metaplasia may have a premalignant potential.[43,44] Pathogenesis of both esophageal and gastric cardia adenocarcinomas is likely to be associated with specialized intestinal metaplasia. While the relationship of the specialized intestinal metaplasia and esophageal adenocarcinoma is well recognized,[22,40-42] the pathogenesis of specialized intestinal metaplasia in the cardia and its importance in cancerogenesis is still not well defined.

Intestinal metaplasia can be recognized by the presence of goblet cells that are interspaced by numerous

Table 1. Summarized data on prevalence of intestinal metaplasia the cardia and its relationship to GERD, gastritis and Helicobacter pylori in patients without endoscopically apparent BE

References	n	Intestinal metaplasia in %	Association of intestinal metaplasia with			
			GERD	Gastritis	Gastric IM	H. pylori
Goldblum	85	22	No	Yes	Yes	Yes
Hackelsberger	315	13.4	No	Yes	Yes	Yes
Morales	93	24	No	Yes	Yes	Yes
Trudgill	117	18	No	Probable	Yes	No
Pereira	44	25		Probable	Not mentioned	Not mentioned
Oberg	334	11.7	Yes	No	No	No
Hirota	833	5.3	No	/	/	Yes
Nakamura	103	28	No	Probable	Probable	Probable

Table 2. Biopsy sampling protocols in assessment of carditis and intestinal metaplasia in cardia in the studies of table 1.

Reference	n	Distance from SCJ	Endoscope position	No of biopsy samples
Goldblum	85	0-5 mm	Retroflexed	2
Hackelsberger	315	"immediately"	Not specified	2
Morales	93	Above/across and 2 cm below	Not specified	4
Trudgill	117	"immediately"	Antegrade	3
Pereira	44	"just below"	Not specified	≥ 4
Oberg	334	Not specified	Antegrade/retroflexed	5
Hirota	833	"immediately"	Antegrade	2
Nakamura	103	0-4 cm	Surgical specimens	Multiple

columnar cells.[11,39] Morphologically, intestinal metaplasia in Barrett's esophagus can not be distinguished from that in the stomach. Intestinal metaplasia in the esophagus, as it is described for gastric intestinal metaplasia, can be complete and incomplete types.[39,45] The columnar epithelial cells of the complete IM are well-differentiated, with a brush border. The incomplete-type intestinal epithelium is immature, less differentiated than complete-type epithelium and it is characterized by mucin-producing columnar cells. Mucin histochemistry has shown that intestinal metaplasia in Barrett's esophagus is usually incomplete (type II and III),[39,46] meanwhile type I is the predominant form of intestinal metaplasia found in the stomach.[45] Intestinal metaplasia in Barrett's esophagus is a premalignant condition. Presence of type II and specially type III -usually called "incomplete" intestinal metaplasia, predispose development of adenocarcinoma at a 30-fold increased risk than in the general population.[47]

Can we identify patients with specialized intestinal metaplasia in cardia originating from the esophagus as opposed to the stomach?

Recently, it was suggested that cytokeratin stains could be used to distinguish the origin of the intestinal metaplasia found in the cardia. Ormsby et al.[48] have identified that Barrett's esophagus has a pattern characterized by positivity for cytokeratins 7 and 20. Cytokeratin 7 stains superficial and deep glands, while CK 20 stains only superficial glands. The results of their study in resection material showed a 100% discrimination value between intestinal metaplasia in the Barrett's esophagus compared to intestinal metaplasia in the stomach including the gastric cardia. Based on these findings they conducted a prospective study on endoscopic biopsies. The results were stimulating. In the patients with Barrett's esophagus, the CK 7 and CK 20 stain was positive in 34 out of 35 patients, with sensitivity of 97%. It was also very specific, since none of the biopsy specimens from stomachs with intestinal metaplasia was positive, either for CK 7 or CK 20. This was challenged in a study where CK 7, CK 20, CK 4 and CK 13 were investigated[49]. They found immunostaining with CK 7 not specific for Barrett's esophagus (77%) as it also stains intestinal metaplasia in both the cardia (45%) and corpus (15%). Cytokeratin 20, according to this group, stained intestinal metaplasia positively in 79% of Barrett's patients and 90% in the cardia. They concluded that CK 7 stain might add little to the distinction between cardiac-type mucosa and Barrett's. It seems that combination, rather than the use of a single cytokeratin stain, should be used in order to increase the specificity. Although cytokeratin stains are very promising research tools and may be helpful in distinguishing between Barrett's esophagus and intestinal metaplasia in the cardia, it is still to be found which is the most precise combination.

Another useful method for the same purpose may be an electron microscopy. It was observed that metaplasia of the Barrett's esophagus expresses so called "hybrid cells", that have both microvilli, a property of columnar cells, and ridges, a property of squamous cells on their surface.[50] Even though electron microscopy can yield important information concerning cell ultrastructure, it is an expensive and time-consuming method in everyday clinical practice.

Prevention, early diagnosis and targets for treatment-Do we have a strategy?

The answer to this question is probably negative. Prevention of the development of intestinal metaplasia in the distal esophagus and gastric cardia will theoretically also abolish the risk of developing the gastric cardia carcinoma subsequently. Medical acid suppression is currently the most widely used treatment modality for gastroesophageal reflux disease. On the other hand, one-

week triple regimes are highly effective in eradication of Helicobacter pylori. Furthermore, it has been shown that by eradicating the Helicobacter pylori, the inflammatory process and its consequences can be reversed. However, concerning the inflammation of the gastric cardia, prospective long-term follow-up studies specifically addressing the question of acid suppression or antibiotic treatment for the prevention of intestinal metaplasia are required.

Furthermore, a variety of oncogenes and their products have been examined in normal, metaplastic, dysplastic epithelium as well as in carcinoma tissue. Metaplastic changes seem to be induced or potentiated by mucosal inflammation. Understanding the molecular changes of this process may lead us to the identification of people at risk of developing malignancies.

Until an agreement is reached, close endoscopic surveillance and histology examination of systematically taken biopsy samples remains the most accepted course of action.

What is the surgeon's opinion?

In 1987 Siewert et al.[51] divided carcinoma of gastroesophageal junction into three distinct tumors that can arise within this area. Adenocarcinoma of the distal esophagus (type I), which usually arises from the area of Barrett's esophagus; "real" carcinoma of the cardia (type II), arising from the epithelium of the gastroesophageal junction and subcardial carcinoma of the stomach, infiltrating the distal esophagus (type III). While type I is treated by transhiatal radical esophagectomy and type III by transhiatal extended gastrectomy there is still no agreed therapeutic approach concerning type II tumors. It is disputed whether type II carcinoma should be treated as an esophageal or as gastric cancer. In a recent editorial, Siewert pointed out that this interpretation should be close to the oncogenesis of this tumor. Since mutations of p53 gene are much more frequently seen in type I than in type II and III cancers which brings "real" cardia cancer much closer to gastric cancer.[52] Subtotal esophagectomy is associated with higher morbidity and mortality in comparison with extended total gastrectomy. Therefore, he suggested that type II cancer should be treated as gastric cancer.

CONCLUSIONS

Despite improvements in therapy modalities, survival of cardiac cancer has not improved significantly, suggesting that alternative strategies for identifying and treating this condition are needed.

When thinking about implications of the previous discussion to our clinical approach, one thing seems to be crucial: to realize the importance of a precursor, either molecular or histological lesions in the cardia and its differentiation from short segment Barrett's esophagus. Taken together, the currently available data indicate that, to a certain degree, short segments of intestinal metaplasia in the distal esophagus are related to excessive and long-lasting reflux of gastric and duodenal contents in the distal esophagus. In contrast, the demographics of patients with foci of intestinal metaplasia in the gastric cardia differ from those of patients with long or short segments of intestinal metaplasia in the distal esophagus. In addition, the clinical parameters for the diagnosis of gastroesophageal reflux do not support a causal role of gastroesophageal reflux disease in the pathogenesis of intestinal metaplasia in the cardia. Rather, some, but not all, recent reports indicate that intestinal metaplasia in cardia may be related to Helicobacter pylori infection, as has been described, elsewhere in the stomach. Despite its relatively high prevalence and unknown malignant potential, many questions about the prevention and management of intestinal metaplasia in the gastric cardia remain unsolved.

Close endoscopic surveillance of patients presenting intestinal metaplasia at the esophagogastric junction, seems currently to be the only effective means of reducing the increasing mortality rates from gastric cardia carcinoma. Once the diagnosis of carcinoma is established, the only option is surgical resection. However, current approaches of medical intervention aiming to detect and remove potential risk factors are still optional. These include, for the time being, acid suppression treatment, and eradication of Helicobacter pylori, laser or photodynamic ablation of premalignant lesions or endoscopic strip resection.

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