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EDITORIAL

Gastric atrophy, diagnosing and staging

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Abstract

H pylori is now accepted as the cause of gastritis and gastritis-associated diseases, such as duodenal ulcer, gastric ulcer, gastric carcinoma, and gastric MALT lymphoma. The natural history of *H pylori* gastritis includes inflammation progressing from the antrum into the adjacent corpus resulting in an atrophic front of advancing injury leading to a reduction in acid secretion and eventual loss of parietal cells and development of atrophy. Sub-typing intestinal metaplasia has no clinical value to the patient, the pathologist, or the endoscopist. The pattern, extent, and severity of atrophy, with or without intestinal metaplasia, is a far more important predictor than is intestinal metaplasia subtype. The challenge remains to identify a reliable marker that relates to pre-malignant potential.

Key words: Gastric atrophy; Diagnosis; Staging; *H pylori*

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GASTRITIS DUE TO *H PYLORI* INFECTION

H pylori is now accepted as the cause of gastritis and gastritis-associated diseases, such as duodenal ulcer, gastric ulcer, gastric carcinoma, and gastric MALT lymphoma. Overall, two rules are clear: (1) the pattern of gastritis is the major determinant of disease outcome[1,2], and (2) countries with a high prevalence of gastric cancer and gastric ulcer, such as Japan or Peru, have a low incidence of duodenal ulcer[3]. Duodenal ulcer is typically associated with antral predominant gastritis, little or no atrophy and normal or increased acid secretion[4-7]. Gastric ulcer and intestinal gastric cancer are typically associated with extensive gastritis, widespread intestinal metaplasia and hypo- or achlorhydria[3,4,8,9]. However, both rules can be broken[9,10]: (1) wide spread intestinal cancer has been documented in the corpus of Korean duodenal ulcer patients, and (2) both diseases (duodenal ulcer and gastric cancer) are frequent diagnoses in dyspeptic Korean patients[9,10]. One of the keys to this apparent paradox is a person's natural acid secretory status.

DUODENAL ULCER AND GASTRIC ULCER REPRESENT TWO ENDS OF ONE DISEASE "*H PYLORI* INFECTION"

Although *H pylori* are found throughout the stomach, in the early stages of disease, *H pylori*-associated inflammation is often mild, superficial, or even absent in the gastric corpus[10,11]. The natural history of *H pylori* gastritis is for the inflammation to progress from the antrum into the adjacent corpus resulting in an atrophic front of advancing injury, leading to a reduction in acid secretion and eventually loss of parietal cells and development of atrophy[10,12,13]. This progression is not inevitable. In the general population it progresses at a rate of 1%-2% per year[12]. The rate of progression of gastritis differs among different countries, different regions of the same country and among different *H pylori*-related diseases[14,15]. Overall, the incidence of gastric cancer is highest in countries and regions with a high incidence of early development of atrophic corpus gastritis[12,16-19] (Figure 1). In contrast, in duodenal ulcer patients, gastritis tends to stay largely confined to the antrum and either does not advance, or spreads very slowly, to involve the gastric corpus[12,20,21]. Atrophic pangastritis with hypochlorhydria is rare or develops sufficiently late in life that the risk of gastric cancer for the population of patients with duodenal ulcer remains low.

The rate of progression of *H pylori* gastritis progression depends on the acid milieu. Thus, *H pylori* corpus gastritis is accelerated in clinical scenarios associated with low acid secretion, such as chronic therapy with proton pump inhibitors, which are widely used in gastro-esophageal reflux disease[8,22-37]. Omeprazole therapy is associated with a reduction in bacterial load, both in the antrum and in the corpus, and a tendency for antral histology to improve and corpus gastritis to either not change or worsen. With omperazole therapy, not only does the corpus mucosa fail to show histologic improvement, but there is a significant progression of the inflammatory reaction deeper within the pit involving the proliferative zone[38].

A person's natural acid secretory status thus appears to determine whether they will develop duodenal or gastric

ulcer disease[39,40] with the acid secretory status appearing to affect both the distribution and severity of *H pylori*-related gastritis. There is some evidence that some cases of duodenal ulcer disease may "burn out" and this has been postulated to be due to the extension of gastritis into the corpus, thus reducing acid secretion to the point where it is no longer possible to sustain an active duodenal ulcer[41]. One possibility is that with continued inflammation, antral atrophy may lead to a sufficient destruction of gastrin producing cells[42] to produce a fall in acid secretion[43,44], which would allow the development of corpus gastritis. In most duodenal ulcer cases, gastritis extends slowly or not at all giving the impression of localization to the antrum[45]. Thus, antral predominant gastritis may in some instances represent an earlier stage of atrophic pangastritis such that these patterns actually represent two ends of the spectrum of "*H pylori* infection" rather than mutually exclusive diseases[10,46,47] (Figure 1).

The rate of progression from gastritis to atrophy varies in different geographic regions related to other environmental factors. While diet is probably the most important factor that reduces acid secretion, other factors such as childhood infections may be very important[10,14,48,49]. The rate of development and the proportion of the population with atrophic gastritis is a critical determinant for the risk of gastric cancer in that population[14,15]. The apparent higher prevalence of concomitant duodenal ulcer and gastric cancer in Korea[46] and the presence of atrophic gastritis with intestinal metaplasia in the corpus of Korean duodenal ulcer patients[10] suggest that in Korea the rate of expansion of the atrophic front is more rapid than in patients in other geographic areas.

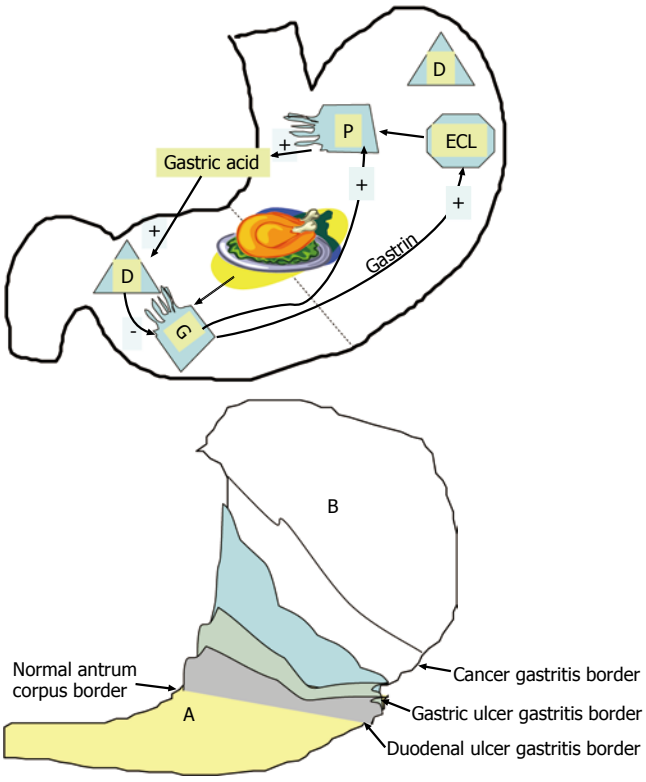

Figure 1 Duodenal ulcer and gastric ulcer represent two ends of one disease "*H pylori* infection". Unlike gastric ulcer patients, duodenal ulcer patients have a long lag period before developing gastric atrophy. Disease progression is dependent on *H pylori* infection (cured/uncured) and other environmental factors such that in some countries DU would be considered protective against the development of gastric carcinoma.

DIAGNOSING AND STAGING GASTRIC ATROPHY

This review only covers the histopathological diagnosis and staging of gastric atrophy; serologic measures are not addressed. The natural history of *H pylori* gastritis is to go through a cascade of events that involves non-atrophic gastritis, atrophic gastritis, and finally dysplasia[50-52]. Atrophy begins at the fundic- or B-boundary line (defined as a margin between the corpus, with complete fundic gland mucosa, and the antrum)[18,53,54] as a sheet of pseudo-pyloric metaplasia with islands of intestinal metaplasia[10,13,55] and shifts proximally such that the antrum appears to expand replacing fundic gland mucosa with advancing atrophic gastritis[18,20,53,56]. Corpus atrophy progresses proximally to variably sized regions of the adjacent greater curve, proximal half of the lesser curve, and neighboring anterior and posterior walls of the corpus[13,18,53,57]. We will address intestinal metaplasia and pseudo-pyloric metaplasia separately.

INTESTINAL METAPLASIA

Because the development of gastric carcinoma is a slow and unpredictable process, and intestinal metaplasia is an easily recognizable marker for atrophy, investigators have suggested that sub-typing intestinal metaplasia using high-iron diamine staining might identify subgroups of patients with different risk potential. Intestinal metaplasia sub-typed as Ⅲ is often considered as a precursor lesion for the intestinal form of gastric cancer[58-61]. In practice, areas of intestinal metaplasia (or a certain sub-type) are generally small and can easily be missed at follow-up[62]. Sampling error is likely the critical factor responsible for the fact that an approximately equal number of studies have suggested that intestinal metaplasia regresses or does not regress after treatment of *H pylori* infection[62-70]. Prior studies suggesting an association of type Ⅲ intestinal metaplasia with the development of gastric cancer[59-61,71] did not take into account the higher prevalence of incomplete intestinal metaplasia (type Ⅲ) in the gastric antrum[13,72,73]. In addition, while type Ⅲ intestinal metaplasia is present in all specimens with intestinal type gastric carcinoma, it can easily be missed in biopsy as it can be present in very small areas[13].

A small percentage of cancer patients can show complete replacement of the antrum mucosa with intestinal metaplasia and have normal appearing oxyntic mucosa[13]. It is unknown if these individuals had normal or reduced acid secretion. Continued inflammation with antral atrophy could possibly lead to sufficient destruction of gastrin producing cells[45], which can result in a fall in acid secretion[74,75]. Alternatively, contiguous sheets of intestinal metaplasia may be unstable epithelium especially upon exposure to carcinogens.

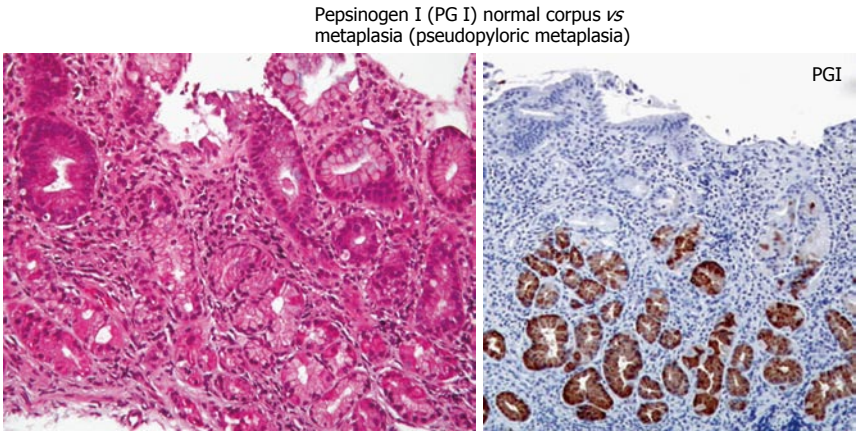

Figure 2 The diagnosis of pseudopyloric metaplasia can be facilitated by using pepsinogen I immunostain. Pepsinogen I (PG I) is localized in chief cells, mucous-neck cells and transitional mucous-neck/chief cells of the human fundic mucosa[78] and is negative in antral gland cells.

Table 1 The diagnosis of pseudopyloric metaplasia can be facilitated by using pepsinogen I immunostain

	Pepsinogen Ⅰ (PG Ⅰ)	Pepsinogen Ⅱ (PG Ⅱ)
Chief cells	Positive	Positive
Mucous neck cells	Positive	Positive
Antral gland cells	Negative	Positive

Pepsinogen I (PG Ⅰ) is localized in chief cells, mucous-neck cells and transitional mucous-neck/chief cells of the human fundic mucosa[78]; it is not localized in antral gland cells. Pepsinogen Ⅱ, on the other hand is localized in chief cells, mucous neck cells, and antral gland cells.

Overall, it is apparent that it is not currently possible to make recommendations or prognoses based on either a single or multiple biopsies showing sulphomucin in areas with intestinal metaplasia[62,72,76,77]. All data suggest that the extent of mucosal atrophy within a region of the stomach may have a more important relation with the intestinal type of gastric cancer than the presence or type of intestinal metaplasia. While intestinal metaplasia is a form of atrophy that is easy for pathologists to recognize, it is also important to determine whether intestinal metaplasia is present as an isolated patch within non-atrophic mucosa or amidst an atrophic lawn[10,13].

PSEUDO-PYLORIC METAPLASIA

The normal oxyntic mucosa has straight glands composed of tightly packed chief cells, parietal cells, endocrine cells, and mucus cells with a higher ratio of glands to foveola than the antrum. With continuous inflammation, and progressive atrophy, there is a progressive loss of parietal cells. Eventually, the oxyntic mucosa glandular compartment can resemble antral/pyloric glands on H&E exam (pseudopyloric metaplasia). The diagnosis of pseudopyloric metaplasia can be facilitated by using pepsinogen I immunostain (e.g. anti-pepsinogen I from Biogenesis Kingston, NH). Pepsinogen I (PG I) is localized in chief cells, mucous-neck cells and transitional mucous-neck/chief cells of the human fundic mucosa[78]; it is not localized in antral gland cells (Figure 2). Pepsinogen Ⅱ, on the other hand is localized in chief cells, mucous neck cells, and antral gland cells (Table 1). Pseudo-pyloric metaplasia is identified by the presence of mucosa that is phenotypically antrum, stains positive for pepsinogen I, and is anatomically in a region where corpus would be expected[13,55].

Pseudopyloric metaplasia has been described as early as 1959[79] in benign gastric ulcers proximal to the normal border zone (antrum-corpus junction). In fact, prior to the rediscovery of *H pylori*, a proximally advancing atrophic front with pseudopyloric metaplasia was considered part of the normal aging process[18,56]. Following the rediscovery of *H pylori*, a positive association has been demonstrated between the presence of mucous glands in corpus biopsies (pseudo-pyloric or mucous metaplasia) and the age of *H pylori* infected patients. This association was more prevalent in Korea where gastric carcinoma is common[10]. The pattern of atrophy in the form of pseudo-pyloric metaplasia is considered regenerative in nature[80,81] and has been observed in experimental models[82], as well as in gastric remnants following distal gastrectomy with gastroenteric anastomosis[83]. In fact, routine screening for gastric cancer in asymptomatic patients with gastric remnants often reveals pseudo-pyloric metaplasia in oxyntic type mucosa.

STAGING ATROPHY

In staging corpus atrophy, it is important to remember four rules: (1) atrophy begins at the border line (antrum-corpus border); (2) atrophy replaces fundic gland mucosa with both pseudopyloric metaplasia and/or intestinal metaplasia[13,53,84]; (3) the atrophic border extends proximally more rapidly up the lesser curve than the greater curvature such that locations high on the greater curvature are among the last to manifest atrophy[13,53,79,84]; and (4) the presence of a higher density of mucosa mononuclear cells that infiltrate deep into the lamina propria is a predictor for the presence of gastric atrophy[38,85].

In early stages of atrophic gastritis, observed in children[55], the location of the antral-corpus border would be expected to be nearer to the normal anatomic border[10]. As such, the identification of atrophy requires biopsies be taken close to the normal antrum corpus junction[55]. In contrast, the atrophic front (atrophic border) is expected to be more proximal in patients in developing countries, in countries with a high incidence of gastric carcinoma (Figure 1), and within particular groups in developed

countries that have a higher incidence of gastric carcinoma, including the socially and economically disadvantaged[86], with the atrophic border advancing more proximally with age[10]. To note, the cardia is not only a high yield zone for *H pylori*[11], but also both intestinal metaplasia and pseudo pyloric metaplasia have been identified in the cardia of children with early atrophic gastritis[55].

The Sydney system and Updated Sydney system[87] were primarily designed to provide standardization for reports of gastric biopsies. The Sydney system[88] recommended a minimum of two biopsies from the respective gastric compartments to be taken from the anterior and posterior wall. In 1994, the Sydney system for the classification and grading of gastritis was updated. The recommendation was unchanged regarding the need for a minimum of two biopsies from the respective gastric compartments but the location was changed from the anterior and posterior walls to the greater and lesser curves of the stomach[87]. In both instances the sites were chosen arbitrarily. Though the Sydney biopsy sites have proven to provide reliable identification of *H pylori* infection[44,89,90], the sites recommended by the Sydney system can only identify corpus atrophy when it is extensive[10,62,90,91]. The recommended biopsy sites for research studies designed to identify the presence, pattern, or changes in atrophic gastritis over time or following a therapeutic intervention must be carefully selected to ensure that they encompass the advancing atrophic border. The number and sites chosen will therefore depend on the average degree and severity of atrophic gastritis expected in the population[13,55]. Use of a standardized reporting system, such as the updated Sydney system, is useful for biopsy specimens particularly as it promotes the use of a visual analog scale to score mucosal findings. For research we suggest the use of a 6 point scale[92] as it provides finer gradation than the 4 point scale used for reporting clinical specimens[87].

In summary, to increase our likelihood of identifying corpus atrophy, when present, special emphasis should be placed on: (1) targeting biopsy sites to encompass the likely sites of the advancing atrophic border and the cardia[55], (2) consistently including intestinal metaplasia and pseudopyloric metaplasia in our evaluation of corpus biopsies for atrophy[13,87], and lastly, (3) raising our suspicion for corpus atrophy in biopsies with a higher density of mucosa mononuclear cells that infiltrate deep into the lamina propria[38,85].

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