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The gastric precancerous cascade

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Abstract

Invasive gastric carcinoma is preceded by a cascade of precancerous lesions. The first recognized histologic change is active chronic inflammation, which may persist as such: non-atrophic chronic gastritis (no gland loss), or advance to multifocal atrophic gastritis (MAG), the first real step in the precancerous cascade. The following steps are: intestinal metaplasia (first "complete" and then "incomplete"); dysplasia, first low grade and then high grade (equivalent to "carcinoma in situ"). The following step is invasive carcinoma, which is thought to be associated with degradation of the intercellular matrix.

Keywords

dysplasia; gastric carcinoma; intestinal metaplasia; precancerous cascade

INTRODUCTION

Gastric adenocarcinoma of the intestinal type[1] is preceded by a prolonged precancerous process. The link between gastric intestinal metaplasia and cancer was proposed by pathologists in Java and Sumatra in 1938.[2] Comparing gastric specimens from Malay patients with a low frequency of gastric cancer and Chinese immigrants with a high frequency of the neoplasia, they reported that Malay patients had low frequency of 'goblet cell metaplasia' while Chinese immigrants had a high frequency of such metaplasia. Morson reported from England in 1955 that gastric carcinomas arose in areas of intestinal metaplasia.[3] A population-based cancer registry was established in Cali, Colombia in 1962.[4] At that time 65.8% of adults in the city were immigrants, mostly from other parts of Colombia. Birthplace-specific cancer rates were calculated. Gastric cancer incidence rates standardized to the Cali natives (referent = 100) were fivefold higher in immigrants from Nariño in the Southern Andes Mountains than that in immigrants from the coasts.[5] A systematic sampling of 1 500 stomachs obtained at autopsy in Cali was conducted to determine the presence of intestinal metaplasia.[5] Prevalence rates of intestinal metaplasia found at autopsy were approximately fivefold higher (59.6%) in patients born in the high cancer-risk area of Nariño than those in immigrants from the coasts (12.9%), a trend analogous to that of gastric cancer incidence rates between these groups.[5]

Based on these experiences we proposed a model of gastric carcinogenesis in 1975.[6] It postulated that the intestinal type of gastric cancer was the end result of progressive changes in the gastric mucosa, starting with chronic gastritis, followed by multifocal atrophic

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gastritis (MAG) and intestinal metaplasia. The model was updated in 1988 and 1992.[7,8] The following consecutive steps were recognized: normal gastric mucosa → superficial gastritis (later renamed non-atrophic gastritis, NAG)[9] → MAG without intestinal metaplasia → intestinal metaplasia of the complete (small intestine) type → intestinal metaplasia of the incomplete (colonic) type → low-grade dysplasia (low-grade noninvasive neoplasia) → high-grade dysplasia (high-grade noninvasive neoplasia) → invasive adenocarcinoma (Fig. 1). In the following paragraphs the histopathological characteristics of each of these steps will be discussed.

GASTRITIS

Normal gastric mucosa may contain only small numbers of scattered mononuclear inflammatory cells (Fig. 2). Gastritis is characterized by increased infiltration of the lamina propria with mononuclear leukocytes (chronic inflammation) and polymorphonuclear neutrophils (acute inflammation) (Fig. 3). The most frequent cause of gastritis is *Helicobacter pylori (H. pylori)* infection (Fig. 4) and the severity of inflammation may vary according to the infected *H. pylori* strain. Polymorphonuclear neutrophil infiltration (also called activity) is usually associated with *H. pylori* infection in humans. Both mononuclear leukocytes and neutrophils may be seen infiltrating the epithelium, and marked acute inflammation is frequently accompanied with microabscesses (collections of neutrophils in the glandular or foveolar lumen). Another characteristic of chronic gastritis associated with *H. pylori* is the presence of lymphoid aggregates with germinal centers.

The response to Helicobacter infection is of both the innate and adaptive types. Immunodeficient mice infected with *Helicobacter felis* develop an innate inflammatory infiltration, independent of the host immune response. It appears that Helicobacter infection can directly cause a low level of inflammation that can be upregulated by adaptive immune response.[10]

Mononuclear cell infiltration (mostly lymphocytes) associated with infection in humans and their accompanying cytokines are of the pro-inflammatory or T helper-1 (Th1) type: interleukin (IL)-1β, tumor necrosis factor (TNF)-α and interferon (IFN)-γ.[11] Under certain circumstances the Th1-type response can be changed to a Th2 (allergic or anti-inflammatory) type, with the expression of cytokines IL-4 and IL-5. In experimental animals this shift can be achieved with anti-IFN-γ antibodies.[11] In humans, coinfection with intestinal helminths has been associated with high serum immunoglobulin E (IgE) levels and high Th2-associated IgG1 responses to *H. pylori*.[12] We observed increased eosinophilic infiltration in the gastric mucosa of *H. pylori*-infected patients in a group at low risk of gastric cancer (but frequently infected with intestinal helminths) in Colombia.[13] We hypothesize that eosinophils in the gastric mucosa may favor a Th2-biased immune response to *H. pylori* that ameliorates the epithelial damage (and therefore decreases the risk of malignant transformation) promoted by the inflammatory process.

The inflammatory changes may persist throughout the whole precancerous process, but their intensity tends to decrease as the process advances. Since the initial *H. pylori* infection targets a normal mucosa with well-preserved gastric glands, by definition such gastritis is non-atrophic. The outcome of such lesion follows the epidemiological model of causation, modulated by the interplay of three sets of etiological factors: those linked to the infectious agent, the host's genetic susceptibility and those related to the external environment. An extensive review on these factors has been recently published.[14] The NAG may be cured by clearing *H. pylori* infection. Otherwise, it may evolve in two ways: either it remains as non-atrophic or it progresses in severity, leading to damage to the gastric glands, which may eventually disappear. This dichotomy determines whether the gastritis enters in the

precancerous process or not. The presence of virulent factors in the infecting *H. pylori* strain is a known determinant factor of the outcome of the infection. Infection with *cag*-positive *vacA* s1m1 strains is associated with precancerous lesions and the development of gastric cancer, while persistent NAG associated to *cag*-negative *vacA* s2m2 does not increase the risk of cancer. Individuals with a duodenal ulcer, who classically have antral predominant NAG lasting for decades, do not have elevated gastric cancer risk,[15] despite being typically infected with virulent strains.

ATROPHY (GLAND LOSS)

Loss of normal glandular tissue is the first specific recognizable step in the precancerous cascade. Usually it is the result of a prolonged inflammatory process and tends to be multifocal, giving rise to the so-called MAG (Fig. 5). The foci of atrophy are present in the mucosa of gastric antrum and body, and their extension progresses with time.[5] The loss of glands may be followed by fibrosis of the lamina propria. A good indicator of the degree of atrophy is the blood level of pepsinogen I (PGI). It is secreted most prominently by the oxyntic mucosa and therefore blood levels become progressively lower as the loss of oxyntic glands advances. Pepsinogen II (PGII) is secreted by foveolar glands in the mucosa of gastric antrum and body. Its secretion is stimulated by inflammation (such as *H. pylori* infection) and cellular proliferation, both hyperplastic and neoplastic. PGI/PGII is a good indicator of atrophy and to some extent of precancerous lesions.[16–18]

A different type of gastric atrophy which limited to the oxyntic mucosa is part of the pernicious anemia syndrome associated with an elevated gastric cancer risk. This syndrome is mostly observed in Scandinavian and northern European groups and appears to be decreasing in frequency. The gastric lesion associated with pernicious anemia is often called autoimmune gastritis or type A gastritis, and is characterized by a severe, diffuse atrophy of the oxyntic glands and hypochlorhydria, and a normal antral mucosa. This type of atrophy is not considered to be part of the precancerous cascade.

Figure 6 schematically represents the pattern observed in the three classical etiological phenotypes of chronic gastritis.[19] Diffuse corporal atrophy is the type of atrophy seen in pernicious anemia in which antiparietal cell antibodies destroy the oxyntic glands. Antral predominant NAG is associated with duodenal ulcer. MAG displays the precancerous cascade discussed in this article.

INTESTINAL METAPLASIA

This lesion represents a phenotypic change from the normal epithelial cell of gastric mucosa to an intestinal phenotype. Intestinal metaplasia is considered to be an advanced stage of atrophy because the metaplastic glands replace the original glands and chronologically the metaplastic glands appear after the gastric glands are lost. Intestinal metaplasia has been classified on the basis of morphology and enzyme histochemistry in two main types: the small intestine or complete type, and the colonic or incomplete type. The intestinal metaplasia of the complete type is characterized by the presence of goblet cells interspersed among absorptive enterocytes with eosinophilic cytoplasm (expressing the complete set of digestive enzymes such as sucrase and trehalase)[20] and a ‘brush border’ given by large numbers of apical microvilli which facilitate absorption of digested food products. Paneth cells may also been observed (Fig. 7). The change does not appear to be abrupt but is progressive instead, as seen in the changing pattern of mucus secretion. The normal mucins of the stomach, MUC5AC at the surface and MUC6 in deeper glands, are pH neutral, and stained magenta with the periodic acid Schiff reagent. In intestinal metaplasia, acid mucins are observed with Alcian blue staining at pH 2.5, mostly sialic MUC2, and may be seen in

the cytoplasm together with neutral mucins. Other metaplastic cells express only sialic acid mucins.

As the metaplastic changes advance and cover larger areas of the mucosa, a new phenotype is observed in some areas: sulfated acid mucins, stained brown with diamine-Alcian blue stain, normally seen in the large high iron intestine, are expressed. This type of metaplasia has been called ‘colonic’ because it resembles the large bowel phenotype in morphology and mucin expression, and also ‘incomplete’ because the set of digestive enzymes disappear partially or completely. Further, some patients may also re-express gastric (neutral) mucins.[21] Incomplete metaplasia cells, like the normal colon epithelial cells, do not display a brush border and their mucin droplets are multiple and of variable size and shape. Gastric biopsy specimens with intestinal metaplasia frequently contain foci of both complete and incomplete metaplasia (mixed metaplasia). Intestinal metaplasia is in general considered to be a condition that predisposes to malignancy, but the presence of incomplete metaplasia and a higher proportion of this type indicate a higher cancer risk.[22–25] Some investigators consider incomplete metaplasia to be a mild form of dysplasia.[26] In addition to the type of metaplasia, the extension of atrophic/metaplastic changes is another determinant of gastric cancer risk.[17,27] The clonal nature of glands with intestinal metaplasia is debated. A recent study has suggested that gastric intestinal metaplasia is the result of a mutation and the metaplastic glands spread in the mucosa by crypt fission.[28] In addition, there is also evidence in support of the clonal origin of gastric dysplasia from metaplasia.[29]

DYSPLASIA

Dysplasia, also called intraepithelial neoplasia or noninvasive neoplasia, is characterized by a neoplastic phenotype, both in terms of cell morphology and architectural organization. The dysplastic epithelium shows enlarged, hyperchromatic and crowded nuclei, and the cells remain within the bounds of the basement membrane (Fig. 8). Mitoses are frequent. The architecture of the dysplastic tissue no longer preserves well-organized glands: they become irregular in shape, occasionally bifurcated or branching and may develop pseudopapillae. These changes may display a gradual transformation from well differentiated to poorly differentiated and have been classified as low grade or high grade, reflecting the cancer risk of each phenotype. Several classifications of gastric dysplasia exist. The Vienna Classification applies the same nomenclature to precancerous lesions of the entire gastrointestinal tract and is not specific to the stomach.[30] The Padova classification is focused on gastric dysplasia and was developed by an international group of experienced gastrointestinal pathologists after extensive review and discussion of gastric biopsies from Europe, Canada, the USA and Japan.[31] The Padova classification recognizes five categories of lesions, utilizing mostly western nomenclature and grouping them numerically following the prevailing Japanese system: 1, negative for dysplasia; 2, indefinite for dysplasia; 3, noninvasive neoplasia (sub-classified in low grade or high grade); 4, suspicious for invasive carcinoma; 5, invasive adenocarcinoma. This classification was designed to improve communications, especially among pathologists and clinicians, by clearly explaining and discussing the possible interpretation and management of each category.[31]

INVASIVE CARCINOMA

Up to this point the precancerous stages can theoretically be explained by accumulated DNA mutations, similar to the so-called Vogelstein model of colorectal carcinogenesis,[32] but the next stage in the cascade requires the penetration of neoplastic cells into the surrounding stroma (Fig. 9), which is not readily explainable by DNA mutations. Recent evidence suggests that this step demands that the neoplastic cells acquire the capability of degrading the stromal matrix surrounding the neoplastic cells. The search for molecules having the

capacity of degrading the matrix has yielded some interesting results. One such molecule is the receptor for urokinase plasminogen activator which has been found in the invasive edge of gastric tumors as well as in macrophages and neutrophils of those patients.[33] It is not clear what triggers the expression of urokinase plasminogen activator receptor (uPAR). *H. pylori* infection is associated with such expression in the gastric mucosa.

DYNAMICS OF THE CASCADE

The changes over time of the precancerous lesions have been compared to the so-called steady state, in which a constantly flowing current may have limited entries and exits but keeps a steady forward movement. It is not clear if the forward and backward experiences observed with gastric biopsies taken at different times are real or the product of biased sampling of the gastric mucosa. A good example of such dynamics was registered in consecutive gastric biopsies of patients in a high gastric cancer risk area of Colombia.[34] The rates of transition between the first and second biopsies per 100 person-years is shown in Table 1. Rates of transition to more advanced lesions were higher in elder patients.[34]

Establishment of *H. pylori* infection as an etiological factor in every step of the precancerous cascade and as a risk factor for gastric cancer has permitted the development of biomarkers that may identify individuals at increased risk. Although the infection with this organism is extremely common and most colonized persons never develop cancer, an infection with *H. pylori* strains possessing recognized virulence factors is significantly associated with a higher risk for progression of gastric pre-neoplastic lesions.[35] The CagA toxin of *H. pylori* is recognized as an oncoprotein and a new molecular biomarker of cancer risk has been recently proposed among *cag*-positive strains. A DNA motif (AATAAGATA)[36] upstream of the translational initiation site of *cagA* is a determinant of *cagA* expression levels and its presence is associated with more advanced precancerous lesions in a Colombian group.[36]

Chemoprevention trials have shown that intervention with either dietary supplementation with antioxidant micronutrients[37] or curing the *H. pylori* infection[37–39] leads to a significant regression of precancerous lesions.

EPILOGUE

Gastric cancer represents a major health burden worldwide. Its prognosis is dismal in most countries, except in Japan where massive programs of early detection are in place. In most countries the most promising strategy to control the disease is prevention, facilitated by the existence of a prolonged precancerous process. A successful strategy for prevention depends on the identification and understanding of the different stages of the precancerous cascade. The lesion detected earliest is the inflammation of the gastric mucosa, usually linked to *H. pylori* infection. *H. pylori* must be eradicated when detected in the presence of gastritis or precancerous lesions, since virulent strains are linked to progression to adenocarcinoma. The inflammatory changes, although frequent, are not specific and are not associated with increased gastric cancer risk. The next stage in the cascade is the loss of glands (MAG) that eventually may be replaced by epithelium with intestinal phenotype. The incomplete type of intestinal metaplasia is clearly associated with a high cancer risk. It has been considered a low-grade dysplasia by some investigators. The extension of the atrophic or metaplastic changes is also an indicator of cancer risk. It can be evaluated with serum PG levels. The final stage of the process, invasive adenocarcinoma, seems to be linked to molecules that have the capacity to degrade the intercellular matrix, such as uPAR. Biomarkers of advanced stages of the cascade hold the promise of a successful cancer prevention program.

Acknowledgments

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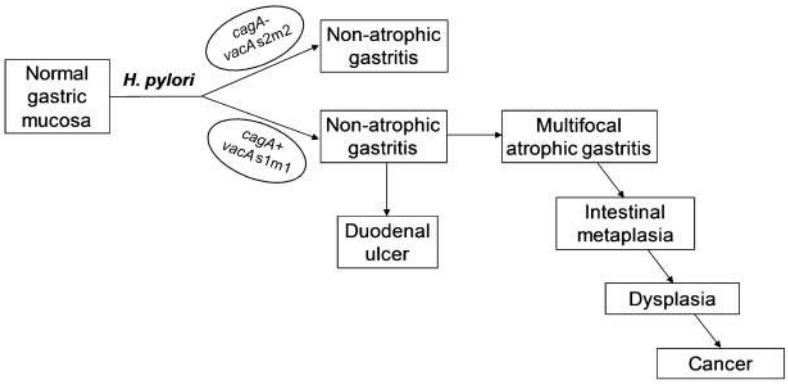

Figure 1.
Schematic representation of the main clinical outcomes of *Helicobacter pylori (H. pylori)* infection. The right side of the figure shows the sequential steps of the precancerous cascade.

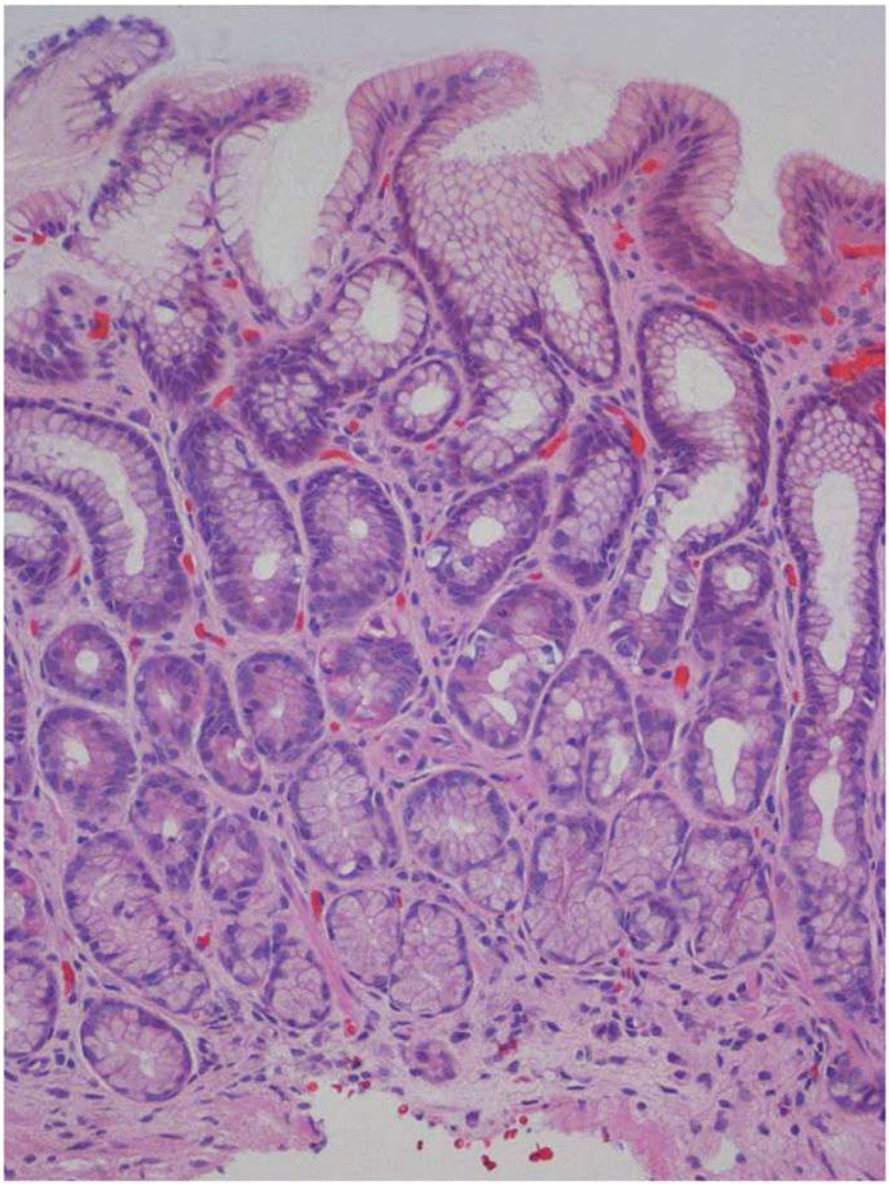

Figure 2.
Normal antral mucosa. Scattered mononuclear cells are normally present in the lamina propria surrounding the glandular structures (HE stain, ×200).

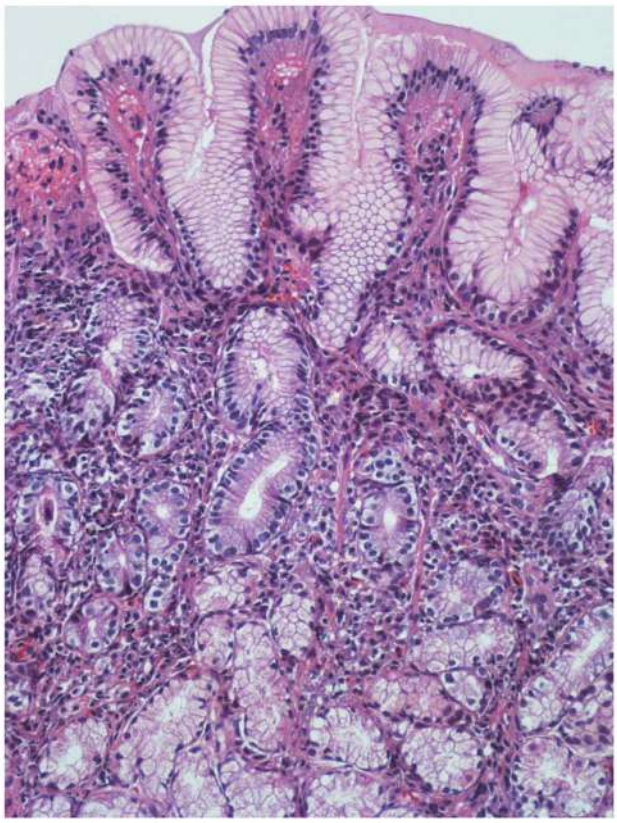

Figure 3.
Nonatrophic gastritis. Antral gastric mucosa with abundant mononuclear leukocytic infiltration in the lamina propria and well-preserved glands (HE stain, ×200).

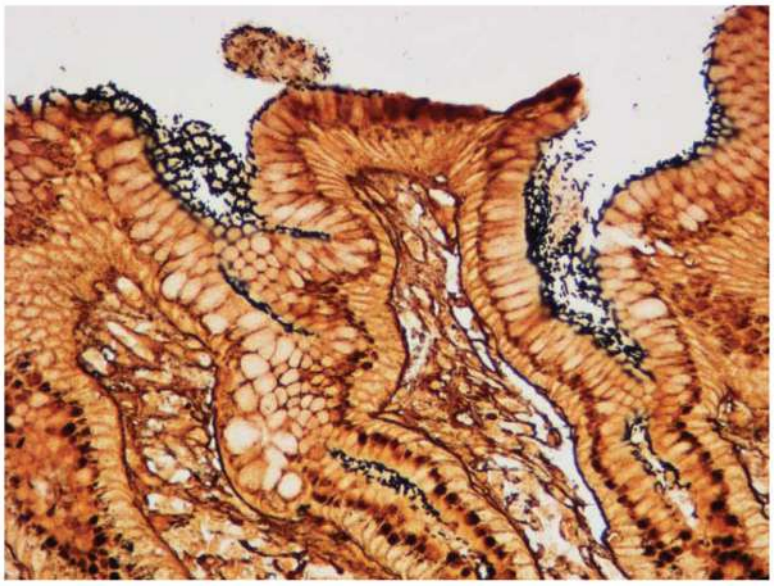

Figure 4.
Gastric antral mucosa colonized with abundant *Helicobacter pylori*. The bacteria are observed in the luminal surface and attached to the epithelium (modified Steiner silver stain, ×200).

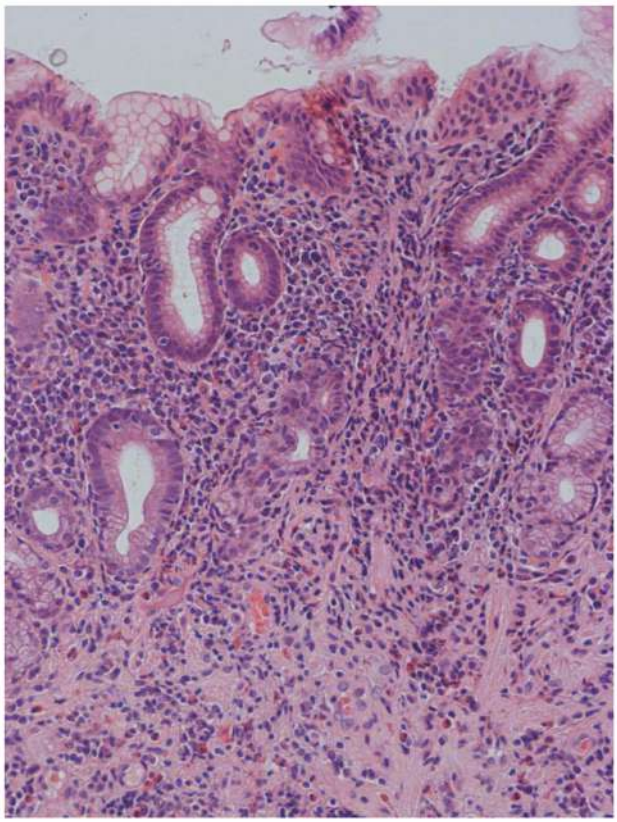

Figure 5.
Multifocal atrophic gastritis without intestinal metaplasia. Antral mucosa with marked mononuclear leukocytic infiltration in the lamina propria and loss of glandular structures, which are replaced by fibrous tissue (HE stain, ×200).

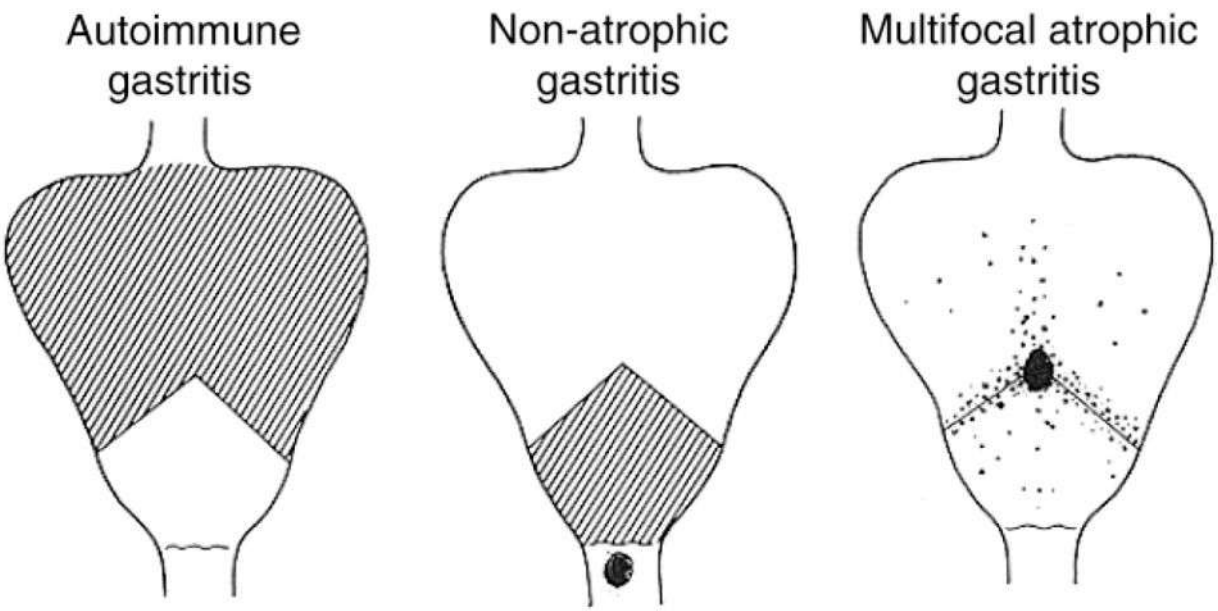

Figure 6.
Diagrammatic representation of the topography of the main types of chronic gastritis. The shaded portions represent the areas involved by gastritis, and the typical location of ulcers is shown. Multifocal atrophic gastritis, shown on the right, is the type of gastritis involved in the precancerous cascade leading to adenocarcinoma of the intestinal type (Diagram reproduced from reference with permission).[19]

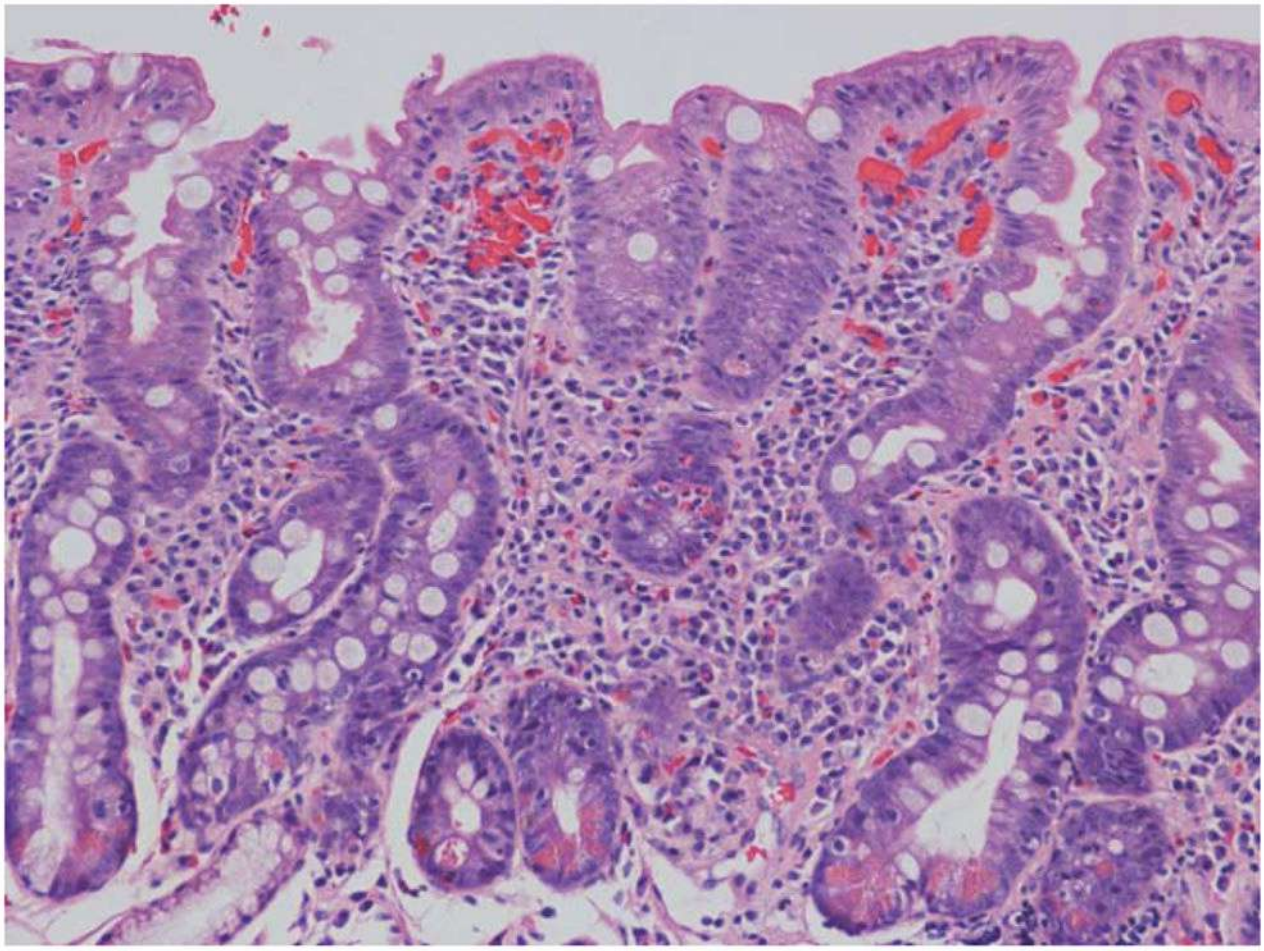

Figure 7.
Complete intestinal metaplasia. The gastric epithelium has been replaced by small intestine-type epithelium, showing eosinophilic absorptive enterocytes with a brush border, interspersed with well-developed goblet cells, and presence of Paneth cells in the deep glands (HE stain, ×200).

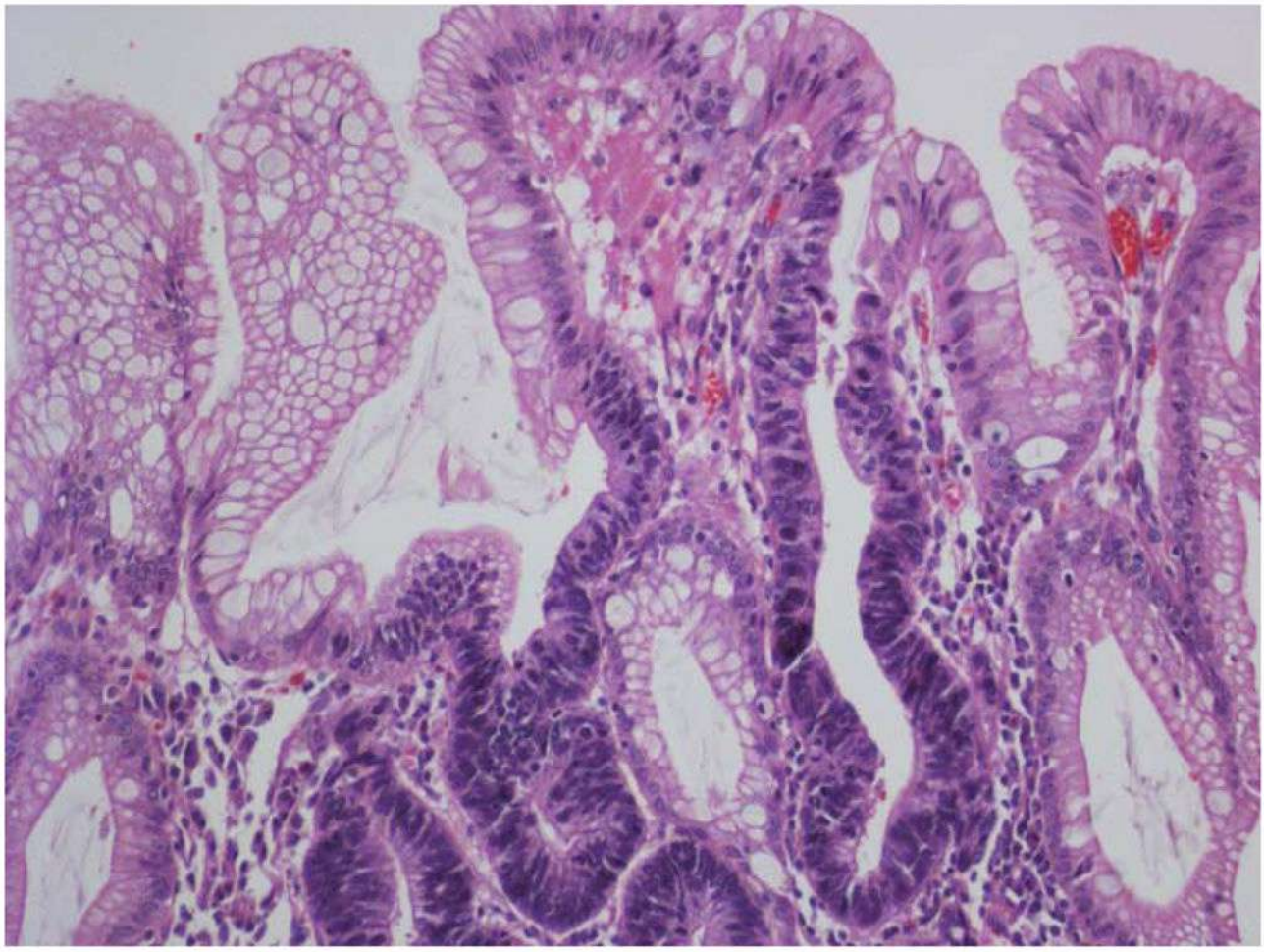

Figure 8.
High-grade dysplasia arising in a background of incomplete intestinal metaplasia. Dysplastic epithelium shows large, hyperchromatic and crowded nuclei with loss of polarity with respect to the basement membrane (HE stain, ×200).

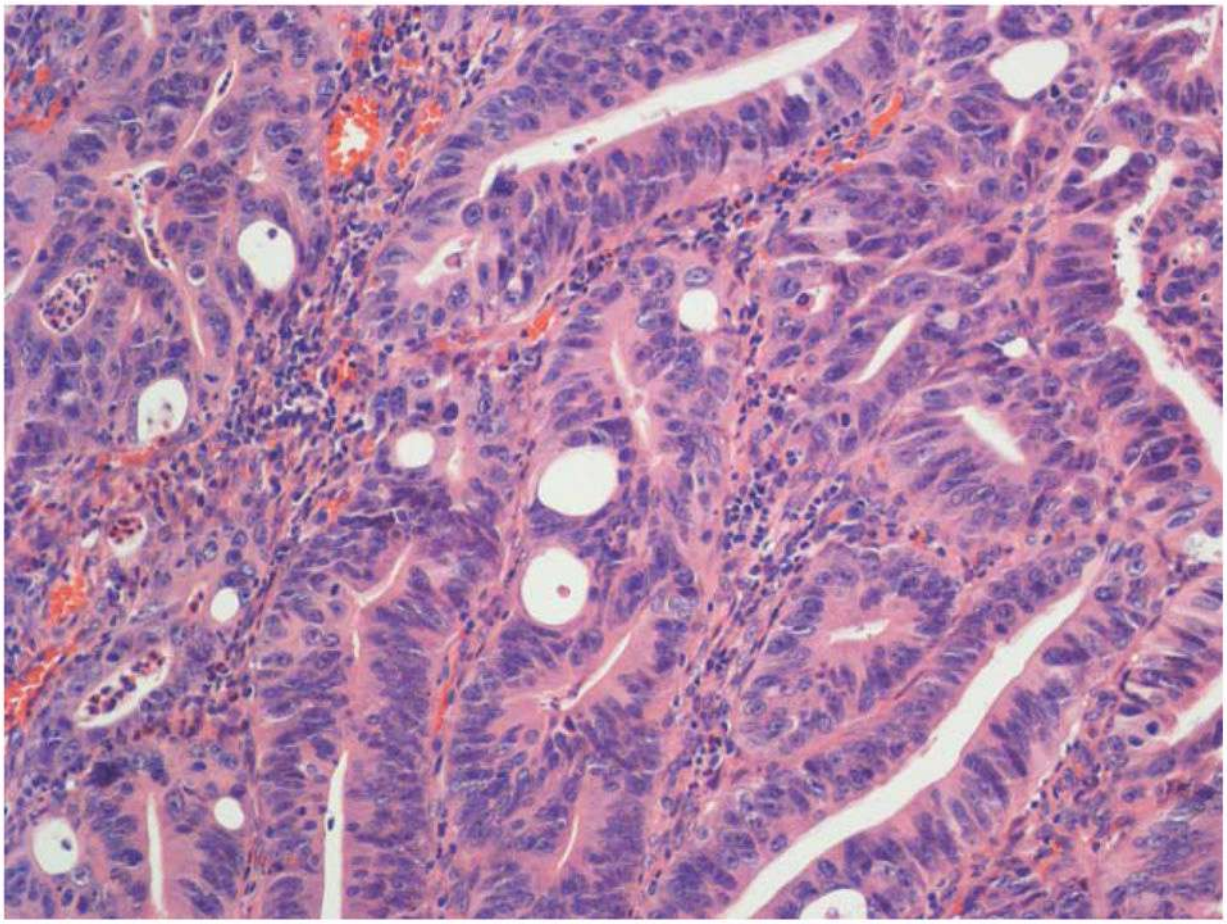

Figure 9.
Adenocarcinoma of the intestinal type. Tumor cells are cohesively arranged in irregular glandular structures infiltrating the stroma (HE stain, ×200).

Table 1

Rate of transition of histopathological gastric lesions between the first and second biopsy per 100 person-years in a Colombian group[34]

Normal or non-atrophic gastritis → atrophy	7.5
Atrophy → non-atrophic gastritis or normal	1.7
Atrophy → intestinal metaplasia	6.7
Metaplasia → atrophy	4.4
Metaplasia → dysplasia	3.2
Dysplasia → intestinal metaplasia	5.7