The gastroenterologist and chronic gastritis in daily clinical practice

William Otero Regino, MD.[1]

[1] Associate Professor of Medicine in the Gastroenterology Unit of the Universidad Nacional de Colombia. Gastroenterologist at the Clínica Fundadores, Hospital El Tunal and Clínica Universitaria Carlos Lleras Restrepo. Bogotá, Colombia.

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Abstract

Chronic gastritis with atrophy and intestinal metaplasia, produced fundamentally by H. pylori, is the principal risk factor for gastric cancer (GC). Despite this, gastroenterologists do not systematically screen patients for GC. Recently a staging system for atrophy and GC has been proposed by the Operative Link for Gastritis Assessment (OLGA). It categorizes stages from 0 to IV. Stages III and IV have the highest levels of risk and merit close attention by physicians. This article reviews the evidence regarding the usefulness of integrating this staging system into daily practice. Based on the results discussed recommendations are made about how to follow up on patients with chronic gastritis.

Key words

OLGA, chronic gastritis, gastric atrophy, intestinal metaplasia, *Helicobacter pylori.*

"Gastritis" is a term that has different meanings. For the general population, and even for many doctors, it describes serious gastrointestinal pain including, discomfort, symptoms of reflux, and even indigestion. For a gastroenterologist it is an endoscopic and histological alteration rather than a clinical entity because it has no manifestations, although the general population believes otherwise. Edema, redness, and erosions can be observed with conventional white light endoscopes. They are histologically related to inflammation, atrophy and intestinal metaplasia (IM). For the pathologist the term has a wider connotation: it means chronic inflammation with increased mononuclear cells, glandular atrophy, *Helicobacter pylori (H. pylori),* polymorphonuclear leukocytes, and complete IM (type I) or incomplete IM (types II and III).

The correlation between endoscopy and biopsy results is 50% (1-3). However, at least 25% of the endoscopically normal cases show histological evidence of gastritis (1-3).

Topographically chronic gastritis can be antral or in both the corpus and antrum (extensive). The first has little or no gastric atrophy, is accompanied by normal or high levels of acid secretion, and is the type of gastritis found in cases of duodenal ulcers. It has a negative association with gastric cancer (GC). In contrast, extensive gastritis in both the corpus and antrum invariably has antral atrophy, hypochlorhydria or achlorhydria and is an alteration which is associated with gastric ulcers and CG (4-7).

Extensive gastritis in the corpus and antrum associated with *Helicobacter pylori (H. pylori)* is a fundamental alteration related to gastric carcinogenesis. Its relationship with this tumor is sufficiently well established for both advanced and early cancers (8-11). However, GC is a multifactorial disease that depends on individual genetic factors, the type *of* H. *pylori,* and other environmental factors such as consumption of fruit and vegetables, too much salt, etc. (8-10). At least 90% of the intestinal type of GC is associated *with* H. *pylori,* but only 1% to3% of those infected will develop the tumor, although all will have chronic gastritis (8, 10 and 11). This implies that *H. pylori* infection is a necessary, but not sufficient, factor in the appearance of tumor. In other

words additional factors that modulate the consequences of infection are required (8-12). The most widely recognized hypothetical model of gastric carcinogenesis is that of Dr. Correa. He describes various progressively pathological states which, starting with superficial chronic gastritis, result in inflammation followed by gastric atrophy, IM, dysplasia and cancer (13).

Although the molecular and biological aspects of chronic gastritis and gastric tumorigenesis are not known with exactitude, there is sufficient information indicating that gastric atrophy is the single most important histological predictor of risk for intestinal type GC (8, and 13-15). Likewise, the progression of gastric inflammation and the appearance of incomplete IM type III are considered to be field cancerization (16). The odds ratio for gastric cancer following incomplete IM type III is 6-17 (17).

Complete IM is morphologically similar to the epithelium of the small intestine with its brush border absorptive villi. Incomplete colonic epithelium is similar to the epithelium of the colon which does not have brush border cells but instead has multiple and irregular mucin vacuoles of variable size (19). IM type I expresses only sialomucins while type III expresses sulfomucins, and type II expresses a mixture of gastric and intestinal mucin (19). At present it is unclear whether these three types of IM follow a chronological sequence (19). Although type III is generally considered to be most significantly associated with CG (20, 21), some authors have different views (22, 23).

Recently another type of metaplasia has been recognized in experimental models infected with *Helicobacter felis.* This type of metaplasia has been called spasmolytic polypeptide-expressing metaplasia (SPEM). It expresses spasmolytic peptide, which apparently comes from transdifferentiation of mature chief cells when there is loss of parietal cells associated with chronic inflammation (24, 25). It is not known whether this type of IM occurs in humans, but if it does the model of Dr Correa might need to be modified.

Despite evidence of increased risk of intestinal type GC when there is gastric atrophy and incomplete IM, a pathology report of chronic gastritis and intestinal metaplasia is not sufficient to clarify to the doctor what is implied in terms of risk, natural history of gastritis, or what type of monitoring an individual patient might require. The problem worsens when the pathologist does not use the nomenclature of a consistent classification system such as the Sydney System (26), but instead reports "mild multifocal atrophic gastritis", "intestinal metaplasia ", " predominantly corporal gastritis," *Helicobacter pylori* active chronic gastritis positive " and other terms according to the individual style of each particular pathologist. These reports are normally tinged with the "Vienna classification". The importance that the endoscopist gives to endoscopic findings suggestive of "chronic gastritis" is attested to by the high frequency of calls for studies of this disease. However, the clinical impact of the pathology report has not been measured, at least not here. Nevertheless, the most important result of a biopsy is proving whether or not *H. pylori* are present. The presence of these bacteria may not always be found with hematoxylin and eosin staining, moreover they are unable to detect atrophy and intestinal metaplasia (26). Consequently, it becomes necessary to use other stains including Giemsa, silver stains and Genta (27). If there is *H. pylori* infection when gastritis is present, the recommendation is to eradicate this infection (9). There is evidence that the elimination of the organism does not reduce the future risk of GC if existing precursor lesions such as atrophy and intestinal metaplasia may have reached the "point of no return ." However the risk is reduced or eliminated when the bacteria are eradicated early, when gastritis is moderate, and when there are few advanced precursor lesions (28-31). Given that no one knows exactly when the "point of no return" occurs, helicobacter pylori eradication is recommended, as it is the only intervention that can reduce the risk of GC in the future. If the above situation is analyzed critically, the gastroenterologist and the patients will feel frustrated, since after eradication of *H. pylori,* the pathology report gives no guidance about what kind of "gastritis surveillance" is needed.

Faced with this dilemma an international group of gastroenterologists and pathologists called OLGA (Operative Link for Gastritis Assessment) recently proposed a staging system for chronic gastritis (32, 33). The OLGA system incorporates experience gained worldwide using the Sydney system (26) such as the clinical utility of informing hepatitis in terms of state or fibrosis. This new system stratifies histological phenotypes of atrophic gastritis into a progressive scale of risk for GC. The lowest state is OLGA 0, and the highest is OLGA IV (Table 1). Similar to the Sydney recommendations five biopsies are taken: two from the corpus 8 cm from the cardia (one from the front wall, and one from the rear wall); two antral biopsies at 2 or 3 cm from the pylorus (one from the greater curvature and one from the lesser curvature); and a biopsy from the angular incision (26). The pathologist's final report should be combined with an etiological hypothesis as to whether the patient is positive or negative for *H. pylori* (32-34). To disseminate this system and strengthen its use, the OLGA group published a tutorial (16). Rugge et al. recently validated this system in a cross-sectional study (34) which demonstrated that all 7 patients with gastric cancer in their study were OLGA stage III and IV, and that the association of these two states with CG was statistically significant.

The OLGA system was used to evaluate atrophic gastritis in Japan, a country with high CG incidence. That evaluation found that 84% of the patients with GC were OLGA III or

Table 1. OLGA staging system with gastric atrophy.

Atrophy score		Corpus			
		No atrophy	Mild atrophy	Moderate atrophy	Severe atrophy
		Score 0	Score 1	Score 2	Score 3
Antrum	No atrophy score 0	Stage 0	Stage I	Stage II	Stage II
	Including angular incision				
	Slight atrophy score 1	Stage I	Stage I	Stage II	Stage III
	Including angular incision				
	Moderate atrophy score 2	Stage II	Stage II	Stage III	Stage IV
	Including angular incision				
	Severe atrophy score 3	Stage III	Stage III	Stage IV	Stage IV
	Including angular incision				

Adapted from (34).

IV: OLGA IV was 56% and OLGA III was 28%. None of the patients with gastric atrophy were OLGA 0. In contrast, most patients with duodenal ulcer were in lower OLGA states: 22% were OLGA 0, and 61% were OLGA I (35). These two studies consistently showed that patients with gastric cancer have higher OLGA stages than those without GC. Sipponem and Graham (36) have also shown that the risk for GC in OLGA Stage IV patients with different phenotypes of atrophic gastritis was from 10 to 90 times greater than for individuals with normal mucosa. This year Rugge et al. published the first evidence showing that the OLGA staging system provides information relevant to the pathological outcome of chronic gastritis and thus for the management of patients (37). They found that all gastric intraepithelial neoplasias were consistently associated with OLGA III and/or IV. Similarly they found a significant inverse correlation between levels of pepsinogen I, the pepsinogen I/II ratio and OLGA system stages of severity.

On the other hand, a classic study of risk stratification by Ohata et al. (15) showed that atrophic gastritis with intestinal metaplasia carries a major risk for GC. For almost eight years these authors followed 4,655 healthy asymptomatic individuals who were diagnosed with *H. pylori* infection by serology and with gastric atrophy based on serum pepsinogens. During follow up 45 patients developed GC (overall incidence rate of 126/100,000). No patients who were negative for *H. pylori* negative and for atrophy developed GC. The hazard ratio (HR) for GC in infected patients increased progressively Patients who were positive for *H. pylori,* but negative for atrophy, had an HR of 7.13 (95% CI 0.95 to 53),. Patients who were positive for both *H. pylori* and atrophy had an HR of 14.8 (95% CI 1.96-107). Finally, patients who were negative for *H. pylori,* but had severe atrophy with IM, had an HR of 61.8 (95% CI 5.6-682). The important results of this study confirm that the GC is very rare in the absence of H. pylori, but that this organism alone, without other factors, is not associated with gastric carcinogenesis. Among those other factors gastric atrophy and IM are the most severe and have the greatest risk of GC.

The CG rate per 100,000 people was totally different for each group. It was zero in Group I, zero, 107 in group II, 238 in Group III, and 871 in group IV. The number endoscopies conducted in one year to find one case of GC was 0/1,000 endoscopies for Group I, 1 / 1,000 for Group II, 1/410 for Group III, and 1/114 for Group IV (38). The findings from these studies suggest that patients with Stage IV should be carefully examined and followed for timely detection of CG. Some experts (38) recommend the following guidelines for monitoring: OLGA Stage IV should have an endoscopic examination every year, OLGA Stage III every two years, and OLGA Stage II should have an endoscopic examination every five years. OLGA Stage I patients do not need to be monitored. Also, risk for CG can be stratified (38) as follows. No risk: patients without *H. pylori* infection and OLGA 0. Minimal risk: atrophic gastritis, OLGA I. Moderate risk: OLGA II. Increased risk: OLGA III and IV. Clearly, to corroborate this prospective studies are needed. However, this interpretation of the different results clearly gives better guidance about how to proceed with these patients than do previous approaches.

CONCLUSIONS

Given the available information, one can conclude that we no longer need to discuss the association between *H. pylori* and GC. The focus should now be on determining the mechanisms of carcinogenesis and on identifying patients at increased risk of GC. Of course, the ideal would be to prevent GC, Theoretically this could be achieved when there are no *H. pylori,* and when enough time has passed so

that no atrophy or IM persists after the infection has been eradicated (39). The best strategy would be real secondary prevention of GC (40) through the eradication of *H. pylori* (41, 42) coupled with risk stratification of atrophy to guide monitoring of patients. This stratification should be based on the OLGA system or another system developed in the future (such as the recently described OLGIM system that replaces gastric atrophy with intestinal metaplasia) (43). In our environment we have found that, among patients with uninvestigated dyspepsia, GC is identified after 30 years of age with a prevalence of 9% (44). Consequently, the local strategy could be upper endoscopy for patients with dyspepsia, investigation of the possibility of *H. pylori* infection, eradication if present, verification of elimination, risk stratification based on OLGA, and individual follow-up of patients according to this information. Today, the OLGA system is an important guide or "roadmap" for decision making by gastroenterologists and their patients. Pathology reports should use this system for GC risk stratification. Current knowledge implies that, rather than simply depending on endoscopies aimed at finding early GC, GC screening programs should provide more coverage among high-risk populations to identify GC, atrophy and *H. pylori* infection through the use of serology (pepsinogen I, pepsinogen ratio I/II, antibodies to *H. pylori)*. The strategy of relying on endoscopy is used in some countries, but it does not prevent further risk progression, has little or no preventive role, and does not alter the natural history of chronic atrophic gastritis (38).

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Conflicts of interest

None.

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