Frequency of morphological changes in gastric biopsies associated with *Helicobacter pylori* infection

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DOI: https://doi.org/10.36104/amc.2021.1987

Abstract

Introduction: morphological changes associated with gastric *H. pylori* infection have been reported, such as chronic superficial gastritis, atrophic gastritis, follicular gastritis and intestinal metaplasia. Importance: Gastric atrophy and metaplasia are part of the cascade of histological changes that lead to gastric cancer.

Methods: a retrospective cross-sectional study analyzing patients with dyspepsia; gastric endoscopy and biopsies were conducted during their exams. The presence or absence of *H. pylori* infection was documented along with the morphological changes present.

Results: a total of 127/166 cases were positive for *H. pylori* infection on gastric biopsy (76.5%), and 39/166 cases were negative for *H. pylori* on gastric biopsy (23.4%). The average age was 45.38 years, 80/127 (63%) were female, 61/127 had superficial chronic gastritis (48%), 43/127 (33.87%) had nodular gastritis, 7/127 (5.5%) had gastric atrophy, and 7/127 (5.5%) had intestinal metaplasia. Of the biopsies which were negative for *H. pylori*, 5/39 (12.8%) had a diagnosis of atrophy, and 4/39 (10.2%) had a finding of metaplasia. in those with a diagnosis of atrophy

Conclusions: the morphological changes found in gastric biopsies are similar to those reported in the international literature. Atrophy, and especially intestinal metaplasia, are morphological changes associated with *H. pylori* infection, and, in turn, risk factors for developing gastric cancer, which were documented in our study. There are *H. pylori*-negative cases with superficial atrophic and metaplastic changes; thus, it is advisable to carry out further studies to completely rule out *H. pylori* infection. **(Acta Med Colomb 2021; 46. DOI: https://doi.org/10.36104/amc.2021.1987).**

Key words: *Helicobacter pylori, atrophic gastritis, intestinal metaplasia, histopathology.*

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Received: 12/VIII/2020 Accepted: 01/III/2021

Introduction

Several morphological changes have been described in the gastric mucosa with *H. pylori* infection, such as: superficial chronic gastritis, atrophic gastritis, gastritis with lymphoid follicle formation or follicular gastritis, and intestinal metaplasia (1).

Superficial gastritis is characterized by infiltration of the gastric mucosa by polymorphonuclear leucocytes and mononuclear cells; this inflammatory phenomenon is important in the survival of *H. pylori,* since the activation of inflammatory cells triggers intracellular events which, as they damage the stomach mucosa, cause the release of nutrients for *H. pylori*. There are several factors which facilitate or promote inflammation of the gastric lining, including interleukin 8 (IL-8), a potent inflammatory mediator which recruits and activates neutrophils in response to cagA positive *H. pylori* genotypes. On the other hand, urease produced by *H. pylori* is a stimulant for mononuclear phagocyte activation and the production of inflammatory cytokines, in addition to delaying macrophage activity, leading to the formation of megasomes. Likewise, the presence of *H. pylori* plays a fundamental role in the synthesis of reactive oxygen species (ROS) in the gastric mucosa, and it has been noted that the higher the *H. pylori bacterial load, the higher the positive association with ROS and the greater the damage to the gastric mucosa (2-7)*.

Follicular gastritis associated with *H. pylori* infection has several names, including nodular antritis, nodular hyperplasia, and micronodular gastritis, and it is characterized by a strong inflammatory reaction which establishes an intense mononuclear infiltrate and the formation of lymphoid aggregates or follicles (8).

Atrophic gastritis indicates the absence of glands in the gastric mucosa, and it is present in *H. pylori* infections. Its diagnosis is important as it forms part of the cascade leading to gastric cancer; however, there is high inter-observer varia-

tion, especially when there is an inflammatory component that makes it hard to determine gland loss versus displacement due to inflammatory infiltrate (9, 10, 12).

Metaplasia is an adaptive change in which an adult-type tissue is replaced by one which is similar but has different functional characteristics. These changes occur as a result of abnormal stimuli. Intestinal metaplasia associated with *H. pylori* infection is considered to be a premalignant change.

The following are morphological traits of type I intestinal metaplasia: enterocytes with an absorptive border and Paneth cells, and straight glandular crypts with a regular architecture. Incomplete, type II or colonic metaplasia is morphologically characterized by: abundant goblet cells and mucus-secreting columnar cells similar to gastric epithelium known as intermediate cells; it lacks Paneth and absorptive cells. There is crypt architectural distortion which is usually branched.

Metaplasia has also been defined as type I intestinal metaplasia with sialomucin secreting goblet cells and non-secretory columnar cells. On the other hand, in type II intestinal metaplasia, or colonic metaplasia, the goblet cells produce sialomucins and, if the columnar cells are secretory, they produce sialomucins, sulfomucins and neutral mucins (13).

Patients with *H. pylori* infection have been studied, determining that the presence of the p-cagA gene is associated with a 3.93 to 10.45 higher risk of intestinal metaplasia of the mucosal surface than that of those who do not express this gene (14).

High levels of nuclear beta catenin may be related to the infection and the development of metaplasia as another predisposing factor, among others; these levels decrease with eradication. It has been reported that treatment of *H. pylori* infection can lead to up to 32.3% regression of intestinal metaplasia (15).

Other genotypic expressions of metaplasia with a colonic phenotype are COX-2 and mAb Das-1. These have been found in tissues adjacent to gastric cancer lesions, and these genotypic changes have been found in 68% of patients without cancer but with *H. pylori* infection, while these same genotypic changes have only been found in 25% of those not infected with *H. pylori*. The detection of these expressions would ultimately identify patients with a higher risk of developing gastric cancer (16).

The precancerous cascade has been described as part of the stages of gastric cancer development, with the following steps: the normal mucosa develops non-atrophic gastritis, then multifocal atrophy and subsequently complete intestinal metaplasia followed by incomplete intestinal metaplasia, later developing low and high-grade dysplasia and, finally, invasive cancer. The progression from one stage to another is determined by *H. pylori* infection (17).

With the previous considerations in mind, this study attempts to describe the morphological alterations present in *H. pylori* positive and negative patients being studied for dyspepsia in the city of Villavicencio.

Methods

Type of study: this is a retrospective, descriptive, analytical cross-sectional study using a medical chart review of patients who were seen by gastroenterology at Clínica Martha in Villavicencio from 2008 to 2017.

Population: the medical charts of 772 patients seen by gastroenterology after being referred by various health insurance companies, and who underwent upper GI endoscopy as part of their workup, were reviewed, and those with a medical chart who met the inclusion criteria were used.

Inclusion criteria: patients consulting for dyspepsia, with no restriction based on age or sex, who had an upper GI endoscopy with a histopathological study, and considering the following histological diagnoses: superficial chronic gastritis, follicular gastritis, the presence of atrophic gastritis and intestinal metaplasia, regardless of the technique employed by the pathology laboratory. In addition, charts with a report of a histological search for *H. pylori* were included, regardless of the result.

Exclusion criteria: patients with gastric cancer, gastric lymphoma, polyps and/or gastric surgery. Those with an *H. pylori*-positive endoscopy without a histological study of the stomach were also excluded.

Data analysis

Description: the population was described using frequency distribution for the main qualitative variables, and measures of central tendency such as the mean and standard deviation for quantitative variables. Fisher's exact test was run to compare the histological findings of *H. pylori*- positive and negative cases.

Ethical considerations: this study is a risk-free study as it is retrospective and observational. The data were obtained from the medical charts. The patients signed a consent, requested by their attending physician, for performing upper GI endoscopy.

Results

Altogether, 166 cases were studied for dyspepsia, with 127 (76.5%) gastric biopsies being positive for *H. pylori* infection and 39 (23.4%) negative for this infection.

The 127 *H. pylori*-positive cases had a mean age of 44.79 years, standard deviation (S.D.): 13.2; and 80 were females (63%).

On histological examination of the *H. pylori* cases, superficial chronic gastritis was found in 61/127 (48%) along with other histological findings (Table 1). Gastritis grading was distributed as follows: mild 7/61 (11.4%), moderate: 24/61 (39.3%), and severe: 4/61 (6.5%); and 26/61 (42.6%) had classifications or descriptions other than gastritis. Age: mean: 44.19, S.D.: 13.41; range: 13-73.

Forty-three patients with nodular gastritis were also found, accounting for 33.87%, with an age range from 15 to 73 years and a mean age of: 46.74; S.D.: 12.69; range:15-73; mode: 47 and a slight female predominance of 25/43 (58%).

Table 1. *Frequency of histological changes associated or not associated with H. pylori.*

Histological findings	*Helicobacter pylori* (+) n=127		*Helicobacter pylori* (-) n=39		Fisher's exact test
	Number	Percentage	Number	Percentage	P value
Chronic gastritis	61	48	27	69	0.009
Nodular gastritis	42	33.9	4	10	0.002
Intestinal metaplasia	7	5.5	4	10.2	0.15
Atrophy	7	5.5	5	12.8	0.08
Source: Prepared by the author.					

For gastric atrophy, 7/127 (5.5%) were found to be *H. pylori*-positive, with an age range from 27 to 80 years, mean: 51.42; S.D.: 16.37.

A total of 7/127 (5.5%) were found to have intestinal metaplasia: Mean age: 47.85; S.D.: 10.93; range: 31-61; complete intestinal metaplasia 2 (1.5%); the type of intestinal metaplasia was not described for the others.

Altogether, 39/166 (23.40%) biopsies were *H. pylori-negative*. Age: mean 47.09. Standard deviation: 13.9; four of the cases had nodular gastritis (4/39,10.2%), five had atrophy (5/39, 12.8%), and four had metaplasia (4/39, 10.2%), two cases were not classified, one case had complete intestinal metaplasia, and one case had incomplete intestinal metaplasia.

Discussion

Ever since the first description by Warren and Marshall, the presence of *H. pylori* has been associated with morphological changes in the gastric mucosa (18, 19)

The Sydney classification has been used to determine the degree of histological inflammation, correlating it with the endoscopic findings. The original Sydney System included two antrum and two body biopsies; in the update, a biopsy of the incisura was considered to be necessary, given that many surface alterations affect the antrum and the incisura. The histological analyses should be separated into gastritis without atrophic or metaplastic changes and those without gastritis (20, 21).

There is no doubt that *H. pylori* infection is responsible for most cases of gastritis. In general, the inflammation caused by the infection is a chronic, inactive gastritis, which means that there is an infiltrate of lymphocytes and plasma cells. The degree of gastritis activity was defined by the presence of neutrophils, being mild when the neutrophils are limited to the lamina propia, moderate when they reach the glandular foveolas, and severe when an ulcer is added to the above changes (22). In addition to the inflammatory infiltrate, there may be lymphoid aggregates, and metaplastic and atrophic areas. The degree of surface involvement varies widely between the body and the antrum. Metaplastic and atrophic areas have been described in up to 20% and their presence virtually excludes an association with a duodenal ulcer. At the same time, they have been associated with early gastric carcinoma, depending on their intensity and topography, with atrophy and metaplasia thought to precede the carcinoma-related changes (23).

Gaviria et al., in their study on the correlation between endoscopic and morphologic changes, found that a low percentage of what was seen endoscopically correlated with histopathological changes, as follows: mild gastritis seen endoscopically was confirmed by histology in 33%; moderate gastritis was histologically confirmed in 42%, while endoscopically-viewed severe gastritis was not correlated with histology (24).

Several studies have included patients with a positive histological study for *H. pylori* infection and the morphological changes are described; in a pediatric study in Brazil, chronic active gastritis occurred in 68.2% with no gastritis grading (25). In Müller's study of 2,019 patients, 66% were found to have *H. pylori* infection, 59% of whom were women, and 77% had chronic non-atrophic gastritis (26).

In the series we presented of *H. pylori*-positive stains, superficial chronic gastritis was found in 48%. The degree of gastritis was: mild 7/61 (11.4%); moderate: 24/61 (39.3%); and severe: 4/61 (6.5%). Of the cases with *H. pylori*-negative stains, superficial chronic gastritis was found in 69%. This histological finding was significantly different between positives and negatives, p= 0.009. The total percentage of *H. pylori*-positive superficial chronic gastritis found is lower than that found in other international studies.

Follicular gastritis in the mucosa and the presence of *H. pylori* has already been documented. In Colombia, it was found in 8.4% of 102 patients under the age of 35 (27). In an Italian study of biopsies in children, antral nodularity was found in 32 out of 77 individuals (41.5%). This finding has been related to CagA+ gene expression and a more severe inflammatory process (28). In Korea, histological nodular gastritis was found in 50.6% of 328 children and adolescents and was associated with intense degrees of inflammation; no association was found with sex or age (29). Kara N et al. studied a total of 358 patients with an average age of 18 (+/ 3) and detected *H. pylori* infection in 59.8%. Endoscopy revealed that the most common change was antral nodularity. Histology showed gastritis in the body and antrum and the prevalence of lymphoid follicles and aggregates was more frequent in the *H. pylori-positive* group (p<0.001) (30). Hayashi S et al. showed that the endoscopic findings of

antral nodularity were associated with histological changes of nodular gastritis in 23% of 211 patients studied, with ages ranging from 23 to 86 years. These findings were more frequent in women, 33%, than in men, 12% ($p<0.01$) (31).

In our series, nodular gastritis was found in 33.87%, with an average age of 46.7 years. This result is more in line with the findings of international studies, since the Colombian results only showed an 8.4% association. It is a common endoscopic finding in our setting, which has coincided well with the histopathological studies; the difference between *H. pylori*-positive and negative cases in this study of nodular gastritis was statistically significant (p=0.002); however, more correlational studies will be needed for our area.

In a Peruvian study of 1,406 adult patients with non-ulcer dyspepsia, 78% of whom were *H. pylori*-positive, gastric atrophy was present in 8.25% (32). In a Mexican study of biopsies performed on children, atrophy was found in 7/82 (8.5%) (33). In the Chinese study of 1,634 children, 21.7% of those who were *H. pylori*-positive were found to have moderate chronic atrophic gastritis, compared with 2.6% of those who were negative (34).

In our study, gastric atrophy was described in 5.5% of the patients (7/127), which was lower than all the series found, both Latin American as well as Asian. The difference in atrophy between *H. pylori*-positive versus negative cases was not statistically significant (p= 0.08). In any case, atrophy will need to be taken into account as a histological finding which necessitates patient follow up, given that we are in a high-prevalence area for gastric cancer (35-37). En la serie que presentamos la atrofia gástrica fue descrita en 5.5% de los pacientes (7/127), siendo más bajo que todas las series encontradas tanto latinoamericanas como asiáticas. No fue estadísticamente significativa la diferencia entre *H. pylori* positivos y negativos en relación con atrofia (p= 0.08). Se deberá tener en cuenta en todo caso la atrofia como un hallazgo histológico que obliga a hacer seguimiento de los pacientes ya que estamos en un área de prevalencia alta del cáncer gástrico (35-37).

Cam S studied a total of 390 pediatric patients and found *H. pylori* infection in 289 (74%), describing gastric metaplasia in 11 (2.8%), and indicating that *H. pylori* eradication in children could decrease the frequency of malignant disease in adulthood (38). Cam S estudió un total de 390 pacientes pediátricos y encontró infección por *H. pylori* en 289 (74%), describe metaplasia gástrica en 11 (2.8%) y da a entender que la erradicación de *H. pylori* en niños podría disminuir la frecuencia de enfermedad maligna en el adulto (38).

With regard to whether *H. pylori* eradication treatment could improve precancerous lesions, Mansour-Ghanaei F found no differences between metaplastic lesions prior to and two years after eradicating *H. pylori,* although other authors have reported improvements. These differences are thought to be due to the time of follow up, the sample size, quantity and location of the biopsies and the histological pattern analyses (39). En relación a si el tratamiento de erradicación *H. pylori* pudiera mejorar las lesiones precancerosas, Mansour-Ghanaei F no halló diferencias entre las lesiones metaplásicas previas y dos años después de erradicar *H. pylori,* aunque otros autores han descrito mejorías, se cree que las diferencias se presentan por el tiempo de seguimiento, el tamaño de las muestras, cantidad y localización de las biopsias y los patrones histológicos de lectura (39).

It has been proposed treating patients with persistent intestinal metaplasia after *H. pylori* eradication using Celcoxib 200 mg for one year may prevent progression or cause regression of the gastric metaplasia (40). Se ha propuesto que el tratamiento de pacientes que persistan con la metaplasia intestinal después de la erradicación de *H. pylori* con Celcoxib 200 mg por un año, puede prevenir la progresión o producir regresión de la metaplasia gástrica (40).

There is agreement in that *H. pylori* bacteria should be eradicated in patients with intestinal metaplasia, but there is no specific agreement in how the *H. pylori*-associated intestinal metaplasia should be followed up, nor what should be done if metaplasia persists after eradicating the bacteria. Pelayo Correa and others propose that, if there is a pathology report showing intestinal metaplasia, *H. pylori* eradication treatment should be given. If the biopsy shows metaplasia but is negative for *H. pylori,* the presence of *H. pylori* should try to be proved by a serological test, and once the infection is confirmed, treatment given. However, what should be done if one or more tests are negative for *H. pylori* bacteria is not made clear (41). Hay acuerdo en que debe erradicarse la bacteria *H. pylori* en los pacientes con metaplasia intestinal, pero no hay acuerdo específico de cómo se debe seguir la metaplasia intestinal asociada a *H. pylori*, tampoco en qué se debe hacer si persiste la metaplasia después de erradicada la bacteria. Pelayo Correa y otros proponen que, si hay un informe de patología con metaplasia intestinal, se debe dar tratamiento de erradicación para *H. pylori*. Si la biopsia tiene metaplasia, pero es negativa para *H. pylori* se debe intentar probar la presencia de *H. pylori* por estudio serológico y una vez comprobada la infección dar tratamiento, sin embargo no se aclara qué conducta se tomaría si una o más pruebas resultan en negatividad para la bacteria *H. pylori* (41).

The extent of metaplasia in the original biopsies should be assessed, determining if it is extensive (meaning that metaplasia is found in biopsies of the body and antrum) and determining if it is incomplete (meaning that it has histological morphology of colonic mucosa). In the event that these changes are not present, follow up is not required, but if the changes are present, or are not clearly described in the report, follow up should be performed with gastric mapping. Se debe evaluar la extensión de la metaplasia en las biopsias originales, determinar si es extensa (lo que significa que la metaplasia esté presente en las biopsias de cuerpo y antro) y también establecer si es incompleta (lo que significa que tenga morfología histológica de mucosa del colon) y en caso que no presente estos cambios no requiere seguimiento pero en caso que los cambios estén presentes

o que no estén descritos claramente en el informe se debe hacer seguimiento con mapeo gástrico.

Atrophic gastritis has been thought to be the initial step in the changes that can lead to gastric cancer. It is associated with acid hyposecretion and low pepsinogen levels, which facilitate the formation of carcinogenic agents. Given the relationship between the extent of the gastritis and low pepsinogen levels, gastritis has been considered extensive if the pepsinogen 1 (PGI) level is <70 μg/L, and if the PGI/PGII ratio is < than 3. If these parameters are present, gastric mapping would need to be done every three years (42, 43).

The follow up proposed by Pelayo Correa is: if the pathology report shows metaplasia and *H. pylori* infection, the *H. pylori* infection should be treated. If the pathology report shows metaplasia but is negative for *H. pylori,* a serological, fecal antigen or breath test should be done, with treatment given to those who are positive on these tests. He also recommends establishing the extent of metaplasia and determining if it is complete or incomplete. If these are present, gastric mapping should be performed in one year and be repeated every three years if there is extensive atrophy and serum pepsinogen is less than 70 μg/L or the PGI/PGIII ratio is less than 3 (44).

In our study, intestinal metaplasia was found in 7/127 *H. pylori*-positive patients (5.5%), with complete intestinal metaplasia in 2 (1.5%), and no report of the type of intestinal metaplasia in the others. In the *H. pylori*-negative cases, intestinal metaplasia was found in 4/39 patients (10.2%), two unclassified, one with complete intestinal metaplasia, and the other with incomplete intestinal metaplasia. No difference was found between *H. pylori*-positive and negative cases with regard to intestinal metaplasia (Table 1); therefore, it would be advisable to follow up with these patients according to the guidelines proposed by the Pelayo Correa team, and not just eradicate the *H. pylori,* since metaplasia is part of the cascade leading to gastric cancer.

In clinical practice, up to 25% of histological tests for *H. pylori* infection may be negative, which may be due to prior treatment with antibiotics, bismuth or proton pump inhibitors; taking aspirin; *H. heilmannii* infection; Crohn's disease or eosinophilic gastroenteritis; and even undetermined causes in cases where all the other factors have been studied and ruled out. We must keep in mind that areas of atrophy and metaplasia may be negative for *H. pylori*. To confirm or rule out the presence of *H. pylori,* the chart should be reviewed to identify the possible causes mentioned previously, and a C-13 urea breath test, *H. pylori* antigen stool test and/or culture should be conducted before considering the case to be negative for *H. pylori (44-46).*

Various studies worldwide have concluded that the classification of gastritis as *Helicobacter pylori*-negative is insufficient, as concluded by Genta and Sonnenberg in their study. Thus, Li et al. suggest that *H. pylori-negative* samples may contain specimens such as *Streptococcus spp*. and *Prevotella spp*., which are responsible for 40% of gastric diseases. Furthermore, Rostami's study also suggests the inadequacy of the *H. pylori*-negative gastritis classification, emphasizing the similarities between gastric disease and celiac disease which make them indistinguishable, but whose treatments are radically different (47-50).

When the medical charts were reviewed, a total of 39 cases of *H. pylori*-negative biopsies were found, representing 23.4% of all those studied for dyspepsia with endoscopy and gastric biopsies. Altogether, 4/39 (10.2%) had a finding of metaplasia, of which two were unclassified, one had complete intestinal metaplasia, and one had incomplete intestinal metaplasia. Therefore, these findings are considered to be important, since these cases can be studied using other diagnostic methods, to determine the presence of *H. pylori* and provide appropriate treatment and follow up.

Study limitations

1. Neither the number nor location of the biopsies was determined for each case, as these two conditions might underestimate the presence of the bacteria.
2. The type of histological staining in each case was not determined, since various stains may be used for histological assessment, including hematoxylin eosin, which is not always reliable when few bacteria are present. There are other stains to identify the bacteria, such as the Warthin-Starry and modified Giemsa stains, and there is no record of whether they were used
3. Prior treatment for *H. pylori* was not determined at the time of endoscopy, nor if the patient received antibiotics for any reason.
4. The use of NSAIDs was not determined.
   - Other methods were not used to determine if the *H. pylori-negative* cases were false negatives.
   - That *H. pylori-negative* cases were an entity unrelated to these bacteria could not be ruled out or affirmed.

Conclusions

The morphological alterations of the gastric mucosa found in this study are similar to those found in international studies.

There was a higher percentage of nodular gastritis than in other Colombian studies.

Atrophy and, especially, intestinal metaplasia are risk factors for gastric cancer which were documented in our study.

Superficial chronic gastritis and nodular gastritis were the morphological changes found to have a statistically significant difference between *H. pylori-positive* and negative cases. However, the clinical significance of this finding must be evaluated through prospective studies in our area.

Forty-two percent of the histological readings describe histological abnormalities which do not coincide with those described internationally for histological interpretation of morphological changes. This may be related to different pathologists interpreting the biopsies. It would be good to

carry out prospective studies with a consensus on histopathological readings.

Since this was a retrospective study, it would be advisable to carry out studies in our area of influence to follow intestinal atrophy and metaplasia.

In cases that are *Helicobacter pylori-negative,* but have morphological alterations such as atrophy and metaplasia, it would be advisable to broaden the medical history to take into account probable associated factors to which the negative histology could be attributed, and to perform complementary tests available in our area of influence to confirm or rule out *H. pylori* infection and then determine treatment and conduct appropriate follow up.

A portion of *H. pylori-negative* cases could be an entity unrelated to *H. pylori* infection, which is currently being studied.

Acknowledgements

To the "GRIVI" research group at the Universidad Cooperativa de Colombia at Villavicencio.

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