

Reactive gastropathy: Frequency in endoscopic biopsies evaluated at the Universidad Nacional de Colombia

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Translation from Spanish to English by T.A. Zuur and The Language Workshop

Received: 28-04-11

Accepted: 11-10-11

Abstract

Reactive gastropathy (RG) is primarily produced by non-steroid antiinflammatory drugs (NSAIDs) and bile reflux. It can occur alone or coexist with other types of chronic gastritis (CG). 5,079 histopathological reports of gastric biopsies from 4,254 patients were reviewed: 825 of them had 2 to 7 follow-up studies. 12.8% of these patients were diagnosed with GR while 63.4% were diagnosed with chronic non-atrophic gastritis (CNAG) and 27.3% were diagnosed with chronic multifocal atrophic gastritis (CMAG). *Helicobacter pylori* infections were found in 61.6% of the cases with CNAG, 51.5% with CMAG, and in 18.5% of cases with GR only ($p < 0.0001$). Among patients suffering from both RG and CNAG 43.9% had *H. pylori* infections. 40.7% of those suffering from both CMAG and RG were infected with *H. pylori*. During monitoring of patients RG diagnoses increased to 22.2% in the second study, 26.7% in the third study, and 28.8% in the fourth through seventh studies. Histological findings of RG in these cases are probably residual following disappearance of inflammatory infiltrates due to treatment.

Key words

Reactive gastropathy, chronic gastritis, *H. pylori*, bile reflux, post gastrectomy status, non-steroid antiinflammatory drugs.

INTRODUCTION

Reactive gastropathy is the current denomination for the diagnostic category of damage generated in the gastric mucosa by action of chemical agents such as non-steroid antiinflammatory drugs (NSAIDs) and by bile reflux (1, 2).

Although tissue damage generated by bile reflux was recognized among patients who had undergone gastric resections (post gastrectomy or gastric stump gastritis) in the mid 20th century (3-5), it was only several decades later that it was designated "chemical gastritis". This name describes the histological changes produced by duodenogastric reflux among patients whose stomachs are intact and who consume NSAIDs. These changes occur predominantly in the antral mucosa. Unless they are masked by damage caused by other coexisting types of gastritis caused

by *Helicobacter pylori* that can dominate the histological history, damage caused by irritating chemicals are characterized by reactive epithelial changes, erosion, ulcers and edema in some cases, congestion, presence of smooth muscular fibers (fibromusculosis) and absence of significant inflammatory infiltrates (Figures 1 and 2) (1, 2, 6, 8). In the updated Sydney System (9), RG is classified in the "Special Gastritis" group. Its clinical manifestations include epigastric pain (exacerbated by ingestion and when patient is in the dorsal recumbent position), nausea, and vomiting of bile in the case of excessive duodenogastric reflux. Endoscopic examinations are characterized by mucosal erythema with erosions or hemorrhage centers that compromise the antral mucosa (5, 8) In the United States and Mexico (8-12) RG constitutes the second most frequent diagnosis after Chronic Non Atrophic Gastritis (CNAG).

In Chile RG occupies third place in frequency after CNAG and chronic multifocal atrophic gastritis (CMAG) (4% of cases) (13). In Colombia, an earlier study conducted by the Department of Pathology at the Universidad Nacional de Colombia looked at 1387 cases of patients who had been diagnosed with chronic gastritis in 1999 and 2000. RG diagnoses accounted for only 2.45% of the cases, while CNAG accounted for 70.7% and CMAG accounted for 26.5% (14).

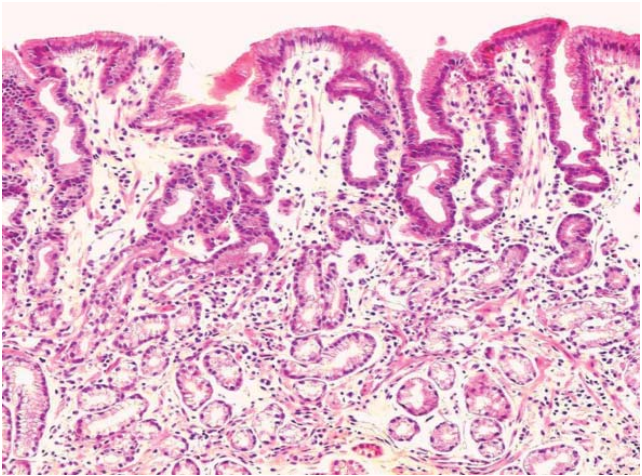


Figure 1. Histological findings of Reactive Gastropathy: regenerative foveolar hyperplasia with winding foveolae, fibromusculosis, edema and only occasional lymphocytes (H&E10x).

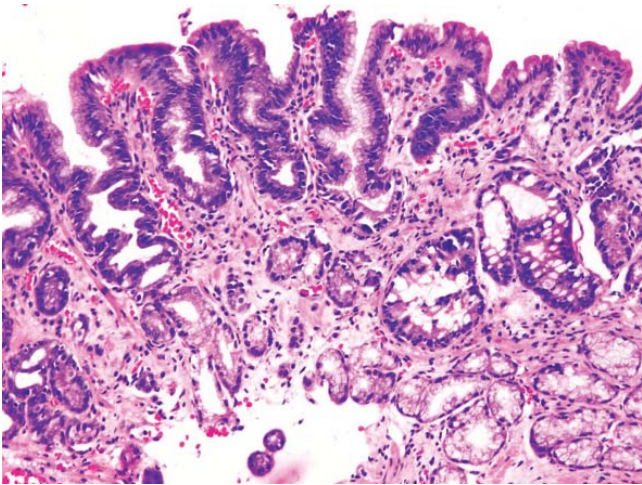


Figure 2. Reactive Gastropathy related to Multifocal Atrophic Chronic Gastritis with histological findings similar to those observed in Figure 1 plus congestion and small focal intestinal metaplasia (H&E 10x).

The objectives of this study are to examine gastric biopsies performed by the Department of Pathology at the Universidad Nacional de Colombia in the period from 2000 to 2008 to determine frequency of RG in light of the perception that its frequency may be increasing, then to

compare it to the frequencies of other types of gastritis, and finally to establish its association with H pylori infection.

MATERIALS AND METHODS

A retrospective descriptive study was performed to establish the proportion of cases with histopathological diagnosis of RG among cases of chronic gastritis in biopsies of patients studied in the Department of Pathology of the Medicine Faculty of Universidad Nacional de Colombia in the period between 2000 and 2008.

To do this all reports in the database of the department that included the terms “Gastritis or Gastropathy” in their diagnoses were selected. These reports had been previously selected from the database’s studies of hematoxylin eosin and giemsa preparations with a check list of criteria for diagnoses of the different categories from the Sydney system (Table 1) (9).

Table 1. Updated Sydney system for chronic gastritis classification.

Non atrophic gastritis
Atrophic gastritis
Autoimmune gastritis
Multifocal atrophic gastritis
Special forms of chronic gastritis
Chemical gastritis or reactive gastropathy (chemical damage)
Gastritis due to radiation
Lymphocytic gastritis
Noninfectious granulomatous gastritis
Eosinophilic gastritis
Other infectious gastritis

Later the proportions of RG cases to cases of other types of gastritis were determined. Cases were categorized by age groups, gender and state of H pylori infection. Chi squared tests were performed for bivariate analysis. Follow-up biopsies (between 2 and 7) identified a numerous group of patients whose results were grouped proportionally and classified in order to compare them with the results of the first study and explore possible differences in the distributions of diagnoses. All the data collected was processed with Microsoft Office Excel 2007 and GraphPad Prism 5.

RESULTS

5,079 histopathological reports from 4,254 patients who had had gastric biopsies that complied with the search term “chronic gastritis or gastropathy” were found. Of these, 825 of them were in follow-up studies and had had more than one biopsy. Table 2 categorizes these follow-up studies.

Table 2. Distribution of follow-up patients according to number of biopsies studied.

No. of biopsies	2	3	4	5	6	7
No. of patients	542	193	60	23	5	2

Cases with only one study and first studies of follow-up cases

Of 4,254 cases, 2,580 patients (60.6%) were women and 1,674 (39.4%) were men. The majority of these patients were between 40 and 70 years old (n=2,502, 58.9%) with the largest single group in their fifties (n=918, 21.6% of cases). 3,935 of these cases were diagnosed with a single type of gastritis, whereas the remaining 319 cases had 2 types of gastritis coexisting for a total of 4,569 diagnoses. The most frequent type of gastritis diagnosed in these series was CNAG (n=2,896, 63.4%) followed by CMAG (n=1,083, 23.7%), RG (n=586, 12.8%), 2 cases of lymphocytic gastritis, one case of granulomatous gastritis and one case of eosinophilic gastritis.

Table 3 shows the distribution of cases and diagnoses by gender and association with *H pylori* infection. It compares cases with a single type of gastritis to those with more than one diagnosis. Significantly fewer RG cases were infected by *H pylori* (18.5%) than were CNAG cases (61.6%; $p<0.0001$, OR 8.483, 95% CI 6.226 to 11.56) or CMAG cases (51.5%; $p<0.0001$, OR 4.588, 95% CI 3.302 to 6.374).

RG also appeared more frequently between 51-70 years old with a similar distribution among men and women. In addition there were 21 cases coexisting with CNAG (2.5%) in patients younger than 21 years of age.

Follow-up cases

Second study

Of the 542 patients with 2 studies, 332 (61.3%) were women, and 210 (38.7%) were men.

The age group with the greatest number of biopsies was between 50 and 70 years of age for both genders (n= 300, 55.4% of cases).

430 of these cases were diagnosed with a single type of gastritis, whereas the remaining 112 were diagnosed 2 types of gastritis for a total of 654 diagnoses.

Among these patients the most frequently diagnosed type of gastritis was CNAG (n= 341, 52.1%), followed by CMAG with 168 patients (25.7%) diagnosed and RG with 145 patients (22.2%).

Table 4 shows the distribution of cases and diagnoses of patients who had two studies by gender and association with *H pylori* infection and compares cases with a single type of gastritis with cases with more than one diagnosis.

Third study

Of the 193 patients with 3 studies, 125 (64.8%) were women, and 68 (32.5%) were men.

Table 3. Distribution of cases with only one study and first follow-up study of cases by gender and association with *H pylori* infections.

	Diagnosis	Cases	Male	Female	<i>H pylori</i>
Cases with only one diagnosis (n= 3,935)	CNAG	2.657 (67,5%)	1.014 (38%)	1.643 (61,8%)	1.636 (61,6%)
	CMAG	1.007 (25,6%)	436 (43,2%)	571 (56,7%)	519 (51,5%)
	RG	271 (6,9%)	115 (41,8%)	160 (58,2%)	51 (18,5%)
Cases with more than one diagnosis (n= 315) *	CNAG + RG	239 (75,9%)	80 (33,5%)	159 (66,5%)	105 (43,9%)
	CMAG + RG	76 (24,1%)	29 (38,2%)	47 (61,8%)	31 (40,7%)

CNAG= Chronic Non Atrophic Gastritis; CMAG= Chronic Multifocal Atrophic Gastritis; RG= Reactive Gastropathy. *4 cases with diagnoses of lymphocytic, granulomatous and eosinophilic gastritis were excluded.

Table 4. Distribution of cases with 2 studies by gender and association with *H pylori* infections.

	Diagnosis	Cases	Male	Female	<i>H pylori</i>
Cases with only one diagnosis (n= 430)	CNAG	274 (63,7%)	101 (36,9%)	173 (63,1%)	120 (43,8%)
	MFACG	123 (28,6%)	59 (48%)	64 (52%)	60 (48,8%)
	RG	33 (7,7%)	12 (36,4%)	21 (63,6%)	9 (27,3%)
Cases with more than one diagnosis (n= 112)	CNAG + RG	67 (59,8%)	23 (34,3%)	44(65,7%)	26 (38,8%)
	CMAG + RG	45 (40,2%)	15(33,3%)	30(66,7%)	21 (46,7%)

CNAG= Chronic Non Atrophic Gastritis; CMAG= Chronic Multifocal Atrophic Gastritis; RG= Reactive Gastropathy.

The age group with the greatest number of biopsies was between 50 and 70 years of age for both genders (n= 125, 64.8% of cases).

131 of these patients were diagnosed with a single type of gastritis, whereas the remaining 62 were diagnosed 2 types of gastritis for a total of 255 diagnoses.

The most frequently diagnosed type of gastritis in this series was CNAG (n= 111, 43.5%), followed by CMAG with 76 patients (29.8%) and 68 patients with RG (26.7%).

Table 5 shows the distribution of these cases and diagnoses by gender and association with *H pylori* infection and compares cases with a single type of gastritis with those with more than one diagnosis.

Four or more studies

Of the 90 patients with 4 or more studies, 61 (67.8%) were women, and 29 (32.2%) were men.

The age group with the greatest number of biopsies was between 50 and 70 years of age for both genders (n= 48, 53.3% of cases).

62 patients in this group were diagnosed with a single type of gastritis, whereas the remaining 28 were diagnosed 2 types of gastritis for a total of 118 diagnoses.

The most frequently diagnosed type of gastritis in this series was CNAG (n= 53, 44.9%), followed by RG with 34 patients (28.8%) and CMAG with 31 patients (26.3%).

Table 6 shows the distribution of these cases and diagnoses by gender and association with *H pylori* infection and

compares the cases with a single type of gastritis with those with more than one diagnosis.

DISCUSSION

Although damage to the gastric mucosa caused by exogenous chemical agents was first described in 1833, histological changes of the mucosa secondary to biliary reflux damage due to gastrectomies were only recognized in the mid 20th century (3-5). RG, which was initially denominated chemical gastritis, only began to be considered a pathological clinical entity at the end of the 1980s (1, 2) when it was included in the update of the Sydney system (9) in the section of special forms of chronic gastritis of which it is the most frequent type. It is associated with biliary reflux following gastrectomies particularly those using Billroth's operation I and Billroth's operation II (5, 15, 16), biliary reflux with intact stomach (1, 2, 7, 8) especially among patients who have had cholecystectomies (5, 12) and to consumption of non-steroidal anti-inflammatory drugs (2, 7, 8, 10).

RG is histologically characterized by the presence of regenerative foveolar hyperplasia that can adopt a winding aspect, by depletion of the mucosa to the foveolar epithelium, and in some cases by erosions and ulcers. When chronic fibromusculosis occurs it is characterized by congestion, edema but absence of significant inflammatory infiltrates (1, 2). Alterations to the superficial epithelium

Table 5. Distribution of cases with 3 studies by gender and association with *H pylori* infections.

	Diagnosis	Cases	Male	Female	<i>H pylori</i>
Cases with only one diagnosis (n= 131)	CNAG	82 (62,6%)	32 (39%)	50 (61%)	23 (28%)
	CMAG	43 (32,8%)	12 (27,9%)	31 (72,1%)	11 (25,6%)
	RG	6 (4,6%)	3 (50%)	3 (50%)	1 (16,7%)
Cases with more than one diagnosis (n= 62)	CNAG + RG	29 (46,8%)	10 (34,5%)	19 (65,5%)	13 (44,8%)
	CMAG + RG	33 (53,2%)	11 (33,3%)	22 (66,7%)	7 (21,2%)

CNAG= Chronic Non Atrophic Gastritis; CMAG= Chronic Multifocal Atrophic Gastritis; RG= Reactive Gastropathy.

Table 6. Distribution of cases with 4 or more studies by gender and association with *H pylori* infections.

	Diagnosis	Cases	Male	Female	<i>H pylori</i>
Cases with only one diagnosis (n= 62)	CNAG	42 (67,7%)	15 (35,7%)	27 (64,3%)	8 (19%)
	CMAG	14 (22,6%)	1 (7,1%)	13 (92,9%)	0
	RG	6 (9,7%)	2 (33,3%)	4 (66,7%)	1 (16,7%)
Cases with more than one diagnosis (n= 28)	CNAG + RG	11 (39,3%)	3 (27,3%)	8 (72,7%)	5 (45,5%)
	CMAG + RG	17 (60,7%)	8 (47%)	9 (53%)	1 (5,9%)

CNAG= Chronic Non Atrophic Gastritis; CMAG= Chronic Multifocal Atrophic Gastritis; RG= Reactive Gastropathy.

are considered secondary to the local action of reflux components, particularly of biliary acids that make mucin soluble but also to the activity of pancreatic enzymes such as trypsin and to NSAIDs. For example, acetylsalicylic acid in the acid medium of the stomach is found in a non-ionized form which is absorbed by the foveolar cells. Once in the cytoplasm it ionizes due to the neutral pH there and generates cellular damage. Changes in the lamina propria occur because of increased numbers of mast cells induced by biliary acids and to the inhibiting effect of cyclooxygenase with reduction of the levels of prostaglandins E1 and E2. This generates damage to the mucus barrier by diminishing secretions of mucus and bicarbonate associated with the reduction of blood flow in the microvasculature (8, 17, 18). In addition, during the course of post-gastrectomy gastritis advanced states of pseudopyloric metaplasia develop together with atrophy and intestinal metaplasia. These are secondary to inhibition of acid-peptic secretion caused by the removal of gastrin producing cells in the antrum (5-8, 15, 16).

It should be noted that it is not possible to identify an etiopathogenic association with consumption of NSAIDs or biliary reflux in a small proportion of RG cases. Also, not all RG cases present all histological characteristics since we cannot observe foveolar hyperplasia or fibromusculosis in some patients with backgrounds of NSAIDs consumption. These observations emphasize the difficulty of diagnosis particularly in cases in which RG coexists with other types of gastritis (19).

Cases of *H pylori* caused chronic gastritis which have been treated with eradication therapy show progressive diminution of activity after infiltration of inflammatory mononuclear leukocytes and formation of lymphoid aggregates until it completely disappears. Disappearance may occur within 6 months, or in the course of years, depending on the severity of the original inflammatory infiltration. Atrophic and metaplastic changes remain in CMAG cases (20-24) although diminution has sometimes been reported (25-27).

The same sequence of findings in the antrum has been described in cases treated with proton pump inhibitors. Displacement of infiltrates to the fundic mucosa, G cell hyperplasia, expansion of fundic glands with appearance of polyps in some cases, persistence of infection by *H pylori* (28, 29, 30) with initial reports of its displacement to the oxyntic mucosa (31) and risk of atrophy (later refuted) (32, 33). These findings are similar to those observed in early phases of post-gastrectomy gastritis which present pseudopyloric metaplasia, atrophy and intestinal metaplasia (3-5) after some delay.

RG was found in 12.8% of the diagnoses in this study, whereas CNAG was found in 63.3% of cases and CMAG

in 27.3% of cases. Our results show a higher frequency of RG than do the findings of the study done by Palau and colleagues in 2000 (14). This is true even when considering cases in which RG was diagnosed without coexistence with any other type of gastritis. The Palau study showed a frequency of single diagnosis cases of 6.9%. This difference may be partially attributable to underdiagnosis in the first study. Some pathologists may not have considered RG to be a specific nosological entity because it had only recently been described. Also, RG may not have been considered because of the subtlety of its characteristics and fact that at that time various diagnostic categories were habitually excluded in order to arrive at only one diagnosis per case. Since 2001 the diagnostic process in the department has been improved by using a database that not only includes classification of diagnostic categories but also includes a checklist with the criteria for diagnoses for each category.

H pylori infections in RG cases (18.5%) were significantly fewer than in CNAG cases (61.6%) ($p < 0.0001$, OR 8.483, 95% CI 6.226 to 11.56) or in CMAG cases (51.5%) ($p < 0.0001$, OR 4.588, 95% CI 3.302 to 6.374), whereas the numbers of *H pylori* infections increased in cases of coexistence of RG with CNAG (43.9%) and CMAG (40.7%). These findings contrast with those reported in Chile where *H pylori* infections were found in 33.3% of RG cases (13). They differ slightly from the ones found in the Palau study in which *H pylori* infection was found in 80.81% of CNAG cases, 63.3% of CMAG cases and in 14.7% of RG cases (14). These divergences may correspond to differences in the characteristics of the evaluated populations. In this study all patients belonged to the contributive health system (similar to HMOs in the USA) and included a large number of university users with a favorable socioeconomic level (professors, employees, students and employees' families). In contrast, a significant proportion of the population in the Palau study belonged to the subsidized health system and had less favorable socioeconomic conditions. Another recognized influence in histological detection of *H pylori* are the use of antibiotics and proton pump inhibitors which were sold over counter in Colombia until recent years. Still other potential influences may be insufficient sampling of the mucosa, the use of special colorations, and the quality of the histological preparations (34). The coexistence of gastritis caused by *H pylori* and RG increases the risk of developing gastric ulcers because of the synergy of the etiological factors (*H pylori*, NSAIDs and/or duodenogastric reflux) (17-19). In this country in which indiscriminate consumption of NSAIDs is habitual, this risk is possibly greater because of the high frequency of chronic gastritis caused by *H pylori*.

Follow-up studies showed increased RG frequency (Table 7), a finding which is similar to the observations in the study done by Kyzekova and colleagues (35).

Table 7. Comparison of frequency distributions of chronic gastritis in initial and follow-up studies.

Diagnoses/Event	1	2	3	4- 7
NACG (%)	63,3	52,1	43,5	44,9
CMAG (%)	23,7	25,7	29,8	26,3
RG (%)	12,8	22,2	26,7	28,8

In follow-up biopsies the percentages of *H pylori* infections in cases in which only RG was diagnosed ranged between a high of 27.7% for second samples and 16.7% for later samples. In contrast significantly higher percentages were found in cases in which RG coexisted with CNAG (first study: 43.9%, second study 38.8%, third study: 44.8%) and GMAC (first study: 40.7%, second study 46.7%, third study: 21.2%).

We do not know what treatment patients received in follow-ups, but we suppose that they had to receive antibiotic eradication treatment, proton pump inhibitors or their combination. Possibly those treated for peptic ulcer disease and for GMAC were more likely to be treated with antibiotics given the extension of atrophic and metaplastic changes, the presence of dysplasia and other considerations for each particular case.

It is possible that more of the GR cases which tested positive for *H pylori* in follow-ups had been treated with proton pump inhibitors than with eradication treatment. Unfortunately the deficiency of clinical information on this issue prevents us from reaching a definitive conclusion and constitutes an objective for later studies.

It is worth highlighting that the consumption of NSAIDs and biliary reflux should have been implied as etiological agents in cases of RG in the first study. On the other hand, in the follow-up cases the presence of RG findings in the control biopsies may be related, but may also correspond to persistent residual histological changes associated with the diminution or disappearance of the inflammatory infiltration and may not necessarily be due to the action of biliary reflux or NSAIDs even when these findings were diagnosed as RG or chemical gastritis. Although some authors have proposed that the eradication of the *H pylori* could favor the appearance of gastroesophageal reflux by generating inflammatory changes in the cardiac mucosa (36, 37), it does not seem to generate duodenogastric reflux and may even diminish it (38, 39).

CONCLUSIONS

RG is a frequent inflammatory process of the gastric mucosa that accounted for 12.8% of the diagnoses in this study. It seems to have been scorned in the literature in comparison

to GC associated with *H pylori*, as can be seen in the disproportionate amount of attention the latter has received in the literature. RG is associated with NSAIDs consumption, bile reflux or and gastrectomies. It can appear simultaneously with chronic gastritis caused by *H pylori* in cases in which their etiological factors coexist thereby increasing the risk of developing ulcers. The frequency of infection by *H pylori* is greater among patients who have only CNAG or CMAG and among those who have both RG and either CNAG or CMAG. Higher frequencies of histological findings of RG were found among patients who were being treated for chronic gastritis caused by *Helicobacter* and those being followed up. In spite of the name, these cases may correspond to residual changes after the disappearance or diminishment of inflammatory infiltration.

Acknowledgements

Dr. Oscar A. Guevara Cruz MD Associate Professor in the Surgery Department and Clinical Investigations Institute of the Faculty of Medicine at the Universidad Nacional de Colombia for his advice about methodology.

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