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FOCAL ENHANCED GASTRITIS AND MACROPHAGE MICROAGGREGATES IN THE GASTRIC MUCOSA: potential role in the differential diagnosis between Crohn's disease and ulcerative colitis

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ABSTRACT – ***Context and Objectives*** - Focally enhanced gastritis and macrophage microaggregates are found in the upper gastrointestinal involvement of Crohn's disease, and may reflect an underlying defective innate immunity. These features, however, are also described in patients with *Helicobacter pylori* infection. The role of these gastric abnormalities in the diagnosis of Crohn's disease was assessed in a population with high prevalence of *H. pylori* infection. ***Methods*** - Thirty-seven Crohn's disease, 26 ulcerative colitis, and 30 control patients were included. The *H. pylori* status was evaluated by the rapid urease test and histology. The presence of focally enhanced gastritis and macrophage microaggregates was recorded. ***Results*** - Focally enhanced gastritis was present in 24% of Crohn's disease patients, 4% of ulcerative colitis patients and 11.5% of controls, presenting an overall sensitivity and specificity for Crohn's disease of 24% and 88%, respectively. Macrophage microaggregates were found in all groups, but were only detected in ulcerative colitis and controls in association with *H. pylori* infection, with an overall sensitivity and specificity for Crohn's disease of 61% and 69%, respectively. In the absence of *H. pylori* infection, focally enhanced gastritis and macrophage microaggregates were significantly associated with Crohn's disease ($P<0.02$ and $P = 0.001$ respectively). ***Conclusions*** - Focally gastritis and macrophage microaggregates are suggestive of Crohn's disease only in *H. pylori*-negative specimens.

HEADINGS - Crohn's disease. Ulcerative colitis. Gastritis. Macrophages. *Helicobacter pylori*.

INTRODUCTION

Inflammatory bowel diseases (IBD) are comprised of Crohn's disease (CD) and ulcerative colitis (UC), conditions with distinct clinical, histological and endoscopic features[23]. They can, however, share similar genetic, clinical and histopathological features, making it difficult to establish a definitive diagnosis in some individuals. As a result, a subset of patients are labeled as indeterminate colitis or inflammatory bowel disease unclassified (IBDU)[18, 33].

Significant gastroduodenal involvement occurs in between 0.5% to 4% of all patients with CD and is usually associated with distal small bowel or colonic disease[13, 24]. The most recognized criteria for gastric CD include the presence of histological evidence of gastric non-caseating granulomatous inflammation, after the exclusion of other granulomatous diseases; or the presence of an established intestinal CD diagnosis with diffuse gastric inflammation compatible with CD[13, 19]. It is estimated that up to 50% of all patients with established intestinal CD also have histological alterations in the gastric mucosa despite the absence of symptoms or radiological abnormalities[5, 28].

Endoscopic evaluation with biopsies of the stomach is the gold standard for the diagnosis of gastric CD[28]. These endoscopic characteristics, however, are non-specific and usually have a patchy distribution, including mucosal friability, erythema, nodular mucosa (cobblestoning), ulcerations and thickened folds[14]. Even the most characteristic CD histological finding, the non-caseating granuloma, lacks specificity as granulomas can also be found in other granulomatous conditions[34]. The most frequent

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histological abnormality in gastric CD is the presence of *H. pylori (Hp)*- negative focally enhanced gastritis (FEG) which is found in almost 80% of patients with known intestinal CD[9, 13].

FEG consists predominantly of macrophages and lymphocytes associated with macrophage microaggregates (MMs) found in the non-inflamed gastroduodenal mucosa[20, 22]. Nevertheless, the presence of *Hp* infection can also generate a similar pattern of gastritis[10]. It is important, therefore, to rule-out the effect of these bacteria if an association is to be established between FEG and CD. The presence of MMs in non-inflamed normal gastric mucosa, however, is characteristic of CD, regardless of the presence of FEG[37].

In Brazil, there is a high prevalence of *Hp* infection[25, 32] and since *Hp* is associated with several of the histological features recognized in gastric CD, its presence could play a confounding role in the histological diagnosis of IBD patients with gastric involvement. The aim of this study was to determine the clinical utility of the diagnosis of FEG and MMs in the gastric mucosa in an IBD population with an expected high prevalence of *Hp* infection.

METHODS

Ethical considerations

The study protocol was approved by the Ethical Committee of the HUCFF-UFRJ. All subjects gave their informed consent prior to their inclusion in the study.

Study population

Sixty-three consecutive patients with IBD, 37 CD and 26 UC patients were recruited at the gastroenterology outpatient unit of the HUCFF-UFRJ. The diagnosis of IBD was confirmed by standard radiological, endoscopic and histological features. CD and UC patients were classified with respect to disease characteristics according to the Montreal Classification[29]. Inflammation was assessed using the Crohn's disease activity index (CDAI)[2] and the Lichtiger Index[15].

Thirty consecutive control patients with dyspeptic symptoms and a normal gastrointestinal endoscopy were also enrolled at the Endoscopy Unit. One patient with intestinal metaplasia and atrophic gastritis was excluded as these histological findings are associated with a higher histological score and could be misinterpreted as a more intense inflammation according to the Updated Sydney System[7]. In addition, gastric metaplasia and atrophy can underestimate the presence of *Hp* infection[11].

None of the IBD patients or controls had received any antibiotics, non-steroidal anti-inflammatory drugs, bismuth compounds, H_2-receptor antagonists, proton pump inhibitors or chemotherapy for at least 6 months prior to study inclusion. Bleeding disorders, use of anticoagulant agents, and diagnosis of other granulomatous diseases were also considered exclusion criteria.

Endoscopy setting and mucosal specimens

Patients and controls underwent a blinded upper gastrointestinal video-endoscopy and received conscious sedation with midazolam and meperidine. Four gastric biopsies were obtained from the gastric body and antrum with standard biopsy forceps. *Hp* infection was determined by positive rapid urease test and histological analysis, as demonstrated by previous studies[1]. Patients were defined as *Hp*-negative when both tests were negative. Two controls, three CD and one UC patients with only one of the two methods confirming *Hp* infection were excluded.

Histological analysis

Formalin-fixed gastric sections were stained with hematoxylin and eosin for the evaluation of microscopic lesions and with Giemsa for *Hp* detection. Histological inflammation was evaluated by two independent blinded pathologists according to the Updated Sydney System[4, 7, 12]. In this score, parameters were inflammation (mononuclear leukocyte infiltration), gastritis activity (neutrophil infiltration), *Hp* density, the presence of atrophy and intestinal metaplasia. All parameters were graded as absent (0), mild (1), moderate (2), or severe (3). FEG was defined when at least one gland, or foveola, was infiltrated by lymphocytes, monocytes and neutrophils surrounded by normal gastric mucosa, as described by Oberhuber et al.[20]. Three patients, one of each group, were excluded, as the gastric samples were inadequate for analysis.

Immunohistochemistry

Tissue samples were immediately embedded in Tissue-Tek O.C.T. compound (Miles Scientific Laboratories Ltd, Naperville, IL) and snap-frozen in isopentane in a liquid nitrogen bath. Samples were then stored at -80 °C until processing, and cut into 6-µm section in a cryostat maintained at -20°C. Tissue sections were air-dried and fixed for 10 min in a 1:1 solution of chloroform-acetone. Immunologic assessment of the intestinal mucosa was made using indirect immunoperoxidase technique using the primary mouse monoclonal antibody anti-CD68 (1:100) (Dako A/S, Glostrup, Denmark). Briefly, frozen sections were immersed in 0.3% hydrogen peroxide in methanol for 20 min to block endogenous peroxidase activity. After being rinsed in phosphate buffered saline (PBS) containing 0.5% Tween 20 for 10 min, tissue sections were incubated with normal horse serum + BSA 0.1% + Triton 0.1% in PBS solution at room temperature in a humidified chamber for 30 min. Subsequently, sections were incubated overnight with the respective primary monoclonal antibody in a humidified chamber at 4°C. Following, the sections were incubated with secondary biotinylated antibody and then with horseradish peroxidase-conjugated streptavidin (LSAB-DAKO® kit) (Dako A/S, Glostrup, Denmark), both for 20 min at room temperature. Sections were then washed in PBS, and developed using 3,3-diaminobenzidine tetrahydrochloride (Dako A/S, Glostrup, Denmark). Preparations were lightly counterstained in Harris's hematoxylin, dehydrated, and mounted in Permount (Fisher Scientific, Pittsburgh, PA, USA). As a negative control, the treatment with the primary antibody was omitted.

Quantitative assessment

Quantitative analysis of tissue sections (under light microscopy at × 400 magnification) and images were captured using a computer-assisted image analyzer (Image-Pro Plus Version 4.1 for Windows, Media Cybernetics, LP, Silver Spring, MD, USA). Any epithelial and lamina propria cells exhibiting identifiable reactivity distinct from the background were regarded as positive. In the immunoperoxidase studies, percentages of different cell subsets were defined by the number of immunoreactive cells in relation to total cell count (immunoreactive and non-immunoreactive cells) in the lamina propria per millimeter squared (counted in at least five different areas or average sum areas of 0.625 mm² per section). The presence of five to ten CD68-positive cells in close contact, relatively losing their own limits in subepithelial or lamina propria layers were recorded as macrophage microaggregates, according to Yao et al.[37].

Statistical analysis

Statistical analysis was performed using SPSS for windows (version 11.0, SPSS Inc, 1989-1999, USA). Fisher exact test and Yates' corrected chi-square were used to test the association between variables. Statistical differences among the experimental groups were evaluated with one-way ANOVA-test in which pair-wise multiple comparisons were carried out using the Dunnett's T3 test. Correlations between densities of positive cells measured by immunohistochemistry were assessed using Spearman rank correlation coefficient. Values were expressed as means ± SEM. FEG and MM-related sensitivity and specificity with positive and negative predictive values for CD diagnosis were calculated. The level of significance was set at $P<0.05$.

RESULTS

Sample characteristics

Clinical and demographic characteristics of the 57 patients with IBD enrolled in this study (33 CD, 24 UC) are summarized in Table 1. Of the 26 control individuals, 14 were female and 8 were male, and the median age was 42 years old (range: 18-67). Age and gender did not differ significantly among the groups. Disease activity, duration, age at diagnosis, location, and clinical behavior were not associated with any endoscopic, histological, or immunohistochemical finding. Upper gastrointestinal symptoms such as epigastric pain, fullness, heartburn and nausea were present in 45% (95% CI: 0.28-0.63) and 42% (95% CI: 0.20-0.63) of CD and UC patients, respectively, with no correlation with any of the analyzed variables in this study. In terms of treatment, neither the use of steroids nor 5-ASA derivates showed any significant correlation with the densities of macrophages.

H. pylori status and endoscopic findings

Regarding the prevalence of *Hp*, no significant difference was found among the study groups, with 50% (13/26) of controls, 54.5% (18/33) of CD, and 62.5% (15/24) of UC patients being infected. The majority of the IBD patients had either a completely normal endoscopic examination, or the presence of nonspecific gastric findings, Table 2. In the IBD *Hp*-positive population, endoscopic gastric abnormalities were comparable in CD (23%) and UC (27%) patients. However, in the *Hp*–negative IBD population, gastric lesions occurred significantly more in CD (47%) than in UC patients (22%, $P = 0.03$, Table 2).

TABLE 1. Demographic and clinical characteristics of the patients with inflammatory bowel disease

Characteristic	CD (n = 33)	UC (n = 24)
Gender: female/male	20/13	15/9
Median age (range, yrs)	39 (18-65)	44 (21-69)
Disease duration in yrs: mean (range)	6 (0.5-26)	5 (1-18)
Disease activity (%)		
Moderate-severe	17 (51)	1 (4)
Mild	8 (24)	11 (46)
Remission	8 (24)	12 (50)
Current treatment (%)		
Steroids	17 (52)	10 (42)
5-ASA	19 (58)	15 (63)
Thiopurines	9 (28)	6 (25)
Age at diagnosis (%)		
A2: 17-40 yrs	28 (84.8)	
A3: >40 yrs	5 (15.2)	
Disease location: CD (L), UC (E) (%)		
L1: ileal	3 (9)	
L2: colonic	6 (8)	
L3: ileocolonic	14 (42)	
L4: upper GI	10 (30)	
E1: proctitis		5 (21)
E2: left-sided		10 (42)
E3: extensive		9 (38)
Disease Behavior (%)		
B1: inflammatory	5 (15)	
B2: stricturing	12 (36)	
B3: penetrating	16 (49)	

CD: Crohn's disease; UC: ulcerative colitis

TABLE 2. Upper gastrointestinal endoscopic findings in inflammatory bowel disease patients with respect to their *Hp* infection status

Endoscopic finding	Normal	Antrum patchy erythema	Aphtous erosions
Crohn's disease			
All	67% (22/33)	12% (4/33)	21% (7/33)
Hp+	78% (14/18)	6% (1/18)	17% (3/18)
Hp-	53% (8/15)	20% (3/15)	27% (4/15)
Ulcerative colitis			
All	75% (18/24)	21% (5/24)	4 % (1/24)
Hp+	73% (11/15)	20% (3/15)	7% (1/15)
Hp-	78% (7/9)	2% (2/9)	0% (0/9)

Histopathological findings

In all groups, the presence of *Hp* was associated with more inflammation demonstrated by higher histopathological scores. The median histopathological scores of control, CD and UC increased significantly from 1 (0-3), 2 (1-4) and 1 (0-3) in *Hp*-negative biopsies, to 6 (4-8), 5 (2-8) and 6 (4-8) in *Hp*–positive specimens, respectively ($P = 0.008$). When analyzing *Hp*-negative IBD patients, no significant difference in the histological scores was found between CD and UC ($P = 0.26$).

Focally enhanced gastritis (FEG)

FEG was detected in 24% (8/33) of CD patients, in 4.2% (1/24) of UC patients and 11.5% (3/26), of controls, regardless of *Hp* status. In UC and controls, FEG exclusively occurred in the presence of *Hp* infection (Figure 1). This histological finding had an overall sensitivity and specificity for CD of 24% and 88%, respectively. In the *Hp*-negative population, FEG had a sensitivity of 33% and specificity of 100%, with a NPV of 100% (Table 3).

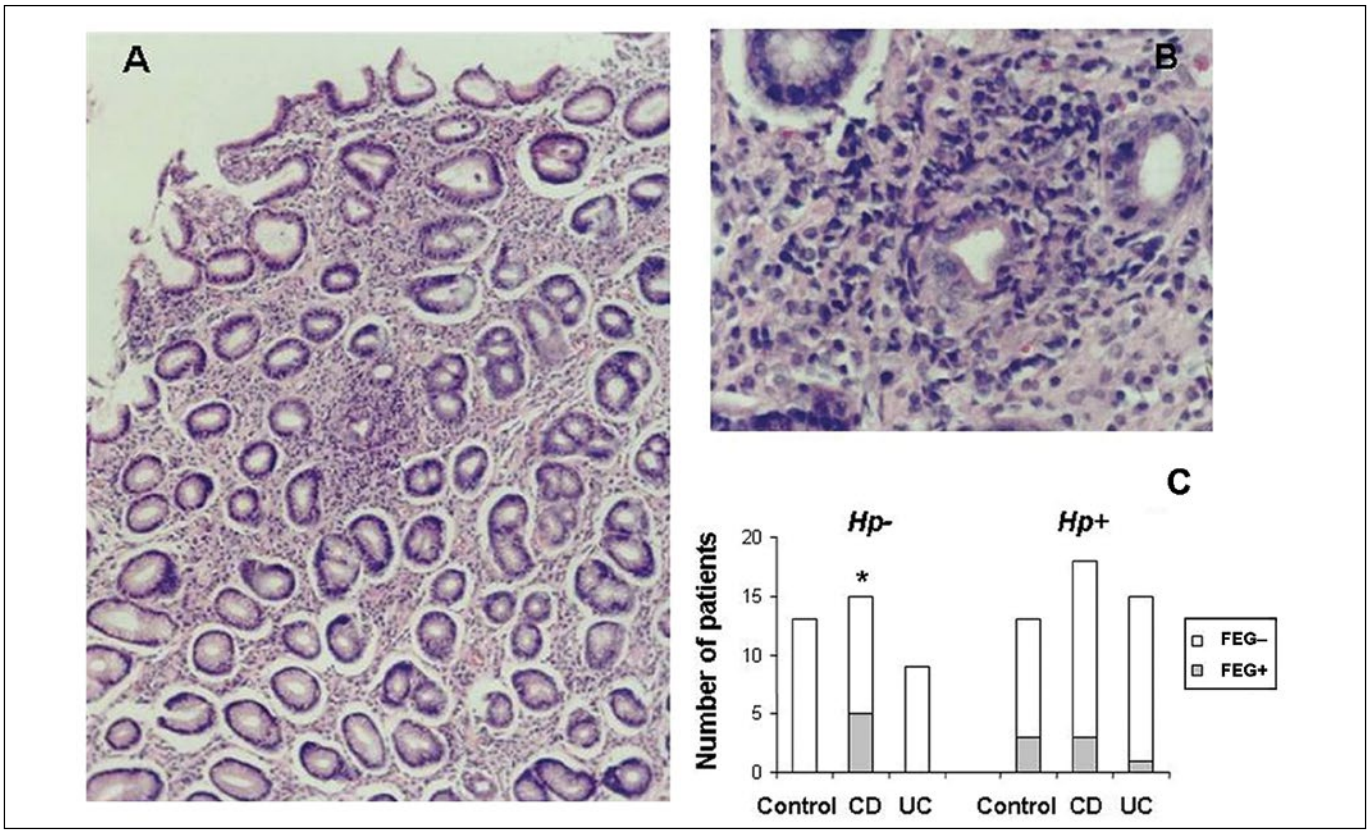

FIGURE 1. H&E staining of the antral gastric mucosa showing a focal inflammatory infiltrate surrounding a gland in a patient with Crohn's disease (CD). (Original magnification ×100) (A). Detail of the previous picture, showing the cellular infiltrate composed of mononuclear cells (Original magnification ×400) (B). Differential presence of focal gastritis in patients with CD, ulcerative colitis (UC), and controls, in relation to *H. pylori* (Hp) infection, was analyzed using chi-square. * $P = 0.014$, as compared with *H. pylori*-negative control and UC patients (C).

TABLE 3. Predictive power of FEG, MM, and FEG+MM, with or without *Hp* infection, as diagnostic markers to distinguish CD from UC.

Marker	Sensitivity	Specificity	PPV	NPV
FEG				
All	24.2 (11.7-42.6)	95.8 (76.8-99.7)	88.8 (50.6-99.4)	47.9 (33.5-62.6)
Hp-	33.3 (12.9-61.3)	100.0 (62.8-100.0)	100.0 (46.3-100.0)	47.3 (25.2-70.5)
MM				
All	60.6 (42.2-76.5)	66.7 (44.7-83.6)	71.4 (51.1-86.0)	55.2 (35.9-73.0)
Hp-	66.7 (38.6-87.0)	88.8 (50.6-99.4)	90.9 (57.1-99.5)	61.5 (32.3-84.8)
FEG+MM				
All	69.7 (51.1-83.7)	66.7 (44.7-83.6)	74.2 (55.1-87.4)	61.5 (40.7-79.1)
Hp-	70.6 (44.0-88.6)	88.8 (50.6-99.4)	92.3 (62.1-99.6)	61.5 (32.3-84.8)

Values are presented as percentages and represent estimated population midpoints with 95% confidence intervals (lower and upper limits in parentheses), for test sensitivity; test specificity; predictive values of the test (PPV: positive predictive value, NPV: negative predictive value). FEG: focally enhanced gastritis; MM: macrophage microaggregate; CD: Crohn's disease; UC: ulcerative colitis; Hp-: *H. pylori* negative; All: both *H. pylori* positive and negative cases.

Macrophage microaggregates (MMs)

Macrophages were diffusely distributed in the gastric mucosa in 57% of specimens, or formed focal subepithelial and lamina propria MMs in 43% of the specimens (Figure 2A). Although MMs were found in all groups, in controls and UC patients they were almost exclusively associated with the presence of *Hp*. Of the 36 specimens showing MMs, 24 (67%) were *Hp*-positive and no significant difference was found among the groups ($P = 0.7$). In contrast, of the 12 *Hp*-negative specimens presenting MMs, 10 were associated with CD, 1 was a control, and the other was a UC patient. In the absence of *Hp* infection, a strong positive association was found between the presence of MM and CD ($P = 0.001$, Figure 2B). This histological finding had an overall sensitivity and specificity for CD of 61% and 69%, respectively. In the *Hp*-negative population, MMs had a sensitivity of 67% and specificity of 89% (Table 3). In addition, the predictive power for the presence of both FEG and MMs, with or without Hp infection, as a diagnostic marker to distinguish CD from UC is also showed in Table 3.

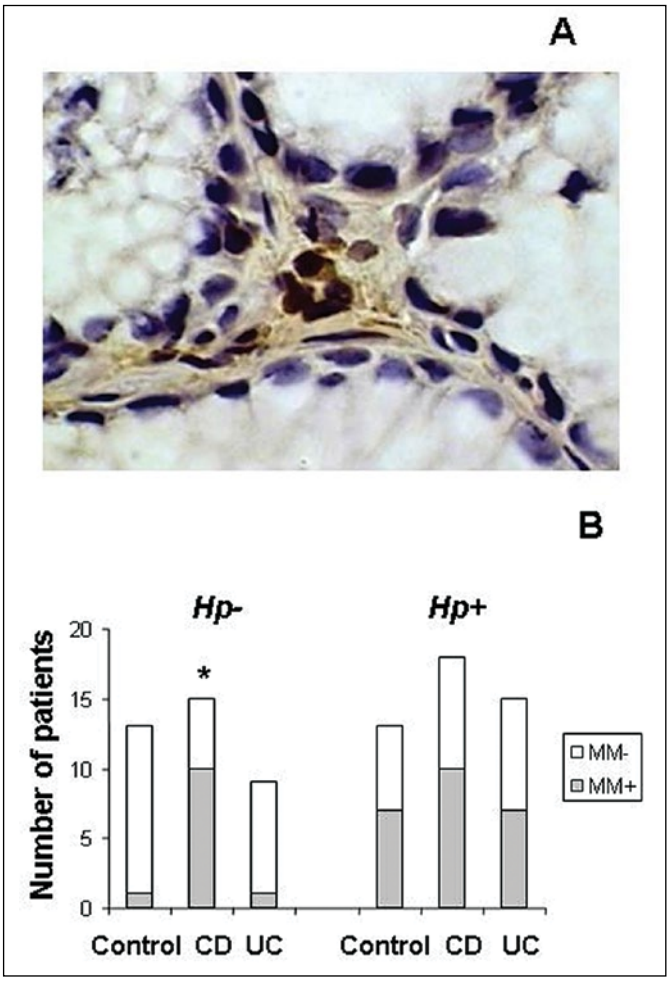

FIGURE 2. Detection of CD68-positive macrophage microaggregates (MM) in the gastric mucosa of a patient with Crohn's disease (CD). The panel shows dark brown immunohistochemical staining for CD68 in mononuclear cells of the gastric lamina propria of a tissue section from a patient with CD (Original magnification ×1000) (A). Differential presence of macrophage microaggregates (MM) in the gastric mucosa of patients with CD, ulcerative colitis (UC), and controls, in relation to *H. pylori* (Hp) infection, was analyzed using chi-square. * $P = 0.001$, as compared with *H. pylori*-negative control and UC patients (B).

Macrophages (CD68+ cells)

In addition to the labeling and identification of MMs, CD68+ cells (macrophages) were also analyzed according to cell density within the lamina propria of antral biopsies in all study groups. A higher CD68+ cell density was associated with *Hp* infection (P=0.001). Although *Hp*-positive CD patients demonstrated a higher CD68+ cell density (16.4±1.4%) compared to controls (10.5 ±1.6%; $P = 0.031$), no significant difference was detected compared to UC patients (14.6 ± 1.7%, Figure 2). Among *Hp*-negative patients, CD68+ cell density was not significantly different between UC (13.1±2.4%), CD (11.1±1.7%), and controls (7.8±2.0%).

DISCUSSION

The diagnosis of IBD is not always straightforward and frequently represents a clinical challenge. In a recent review, Yantiss and Odze described the existence of 5% to 15% of indeterminate colitis among IBD patients[36]. The non-classifiable IBD represents the most noticeable expression of the diagnostic overlap between CD and UC and changes in the diagnosis over time, mostly from UC to CD, are not uncommon and may impact treatment and prognosis. In this regard, before performing colectomy with ileal pouch-anal anastomosis in severe UC patients, is advisable to definitely exclude CD due to the increased risk of surgical complications, disease recurrence and pouch failure if a diagnosis of CD is later recognized[27].

Even though gastric CD can have suggestive features that can help in the diagnosis, they are not pathognomonic. In this regard, many histological characteristics found in gastric CD are also associated with *Hp* infection and this infection can constitute a confounding factor. Accordingly, FEG, for instance, has been observed in the gastric mucosa of *Hp*-positive non-IBD subjects[21]. In our study, therefore, the accuracy of gastric features associated with CD is for the first time evaluated in a population with high prevalence of *Hp* infection.

As expected in a country with high prevalence of *Hp*, the infection ratio in the IBD subjects was higher than previously published[16] and not lower than in controls. In fact, there were no differences in *Hp* prevalence among the study groups. Similarly, there were no differences with respect to endoscopic gastric abnormalities and level of histological inflammation when CD and UC patients were compared. Of note, when the *Hp*-negative IBD population was analyzed, CD patients had more gastric lesions than UC.

FEG has been considered a characteristic histological finding of CD with a variable prevalence (46%-73%) depending on the method employed and the population studied[20, 30].

In this study, FEG was exclusively associated with CD when *Hp* infection was ruled out. This finding suggests that in a population with a high prevalence of *Hp*, the presence of FEG in gastric samples is not necessarily consistent with CD diagnosis, but it can be a discriminatory diagnostic tool in *Hp*-negative IBD patients, reaching a PPV of 100% in this setting. In keeping with these results, studies which had not taken into consideration *Hp* infection have observed that FEG had a low positive predictive value for the diagnosis of CD[35], being not capable of distinguishing between patients with CD and UC[17].

In accordance with the present study, several other investigators have found a higher prevalence of FEG in CD, particularly in children[26], younger patients[31], or in association with colorectal CD[6]. FEG is characterized by a focal infiltration of T-cells and macrophages[8, 20] and it is likely that this accumulation of inflammatory cells may also constitute the basis for the formation of MMs, described in the gastroduodenal mucosa of CD patients[37]. Although MMs were observed in all patient groups, their identification by immunohistochemical staining predominated in CD patients. The remarkable presence of MMs in CD gastric specimens suggests an abnormal and specific distribution of macrophages even in non-inflamed mucosa of these patients. Importantly, as FEG, the presence of MMs in the gastric mucosa was associated with CD diagnosis only in *Hp*-negative individuals.

In the current paper, the impact of the different therapies on the prevalence of FEG and macrophage density was also evaluated. It has been previously suggested that a higher intestinal macrophage density might be associated with intestinal inflammation in CD and that macrophage migration to the inflamed areas could be decreased by 5-ASA therapy[3]. In our study, however, there was no correlation between any medical treatment and FEG, or CD68+ cell density.

In conclusion, the histological gastric abnormalities found in *Hp*-positive IBD individuals are non-specific. In *Hp*-negative specimens, FEG and MMs are associated with the diagnosis of CD. Importantly, these histological abnormalities can be found even in endoscopically normal mucosa without any macroscopic lesions.

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Magalhães Costa MH, Reis BR, Chagas VLA, Nunes T, Souza HSP, Zaltman C. Gastrite focal e microagregados de macrófagos na mucosa gástrica: uso potencial no diagnóstico diferencial entre doença de Crohn e colite ulcerativa. Arq Gastroenterol. 2014,51(4):276-82.

RESUMO - ***Contexto e objetivos*** - Gastrite focal e microagregados de macrófagos são encontradas no acometimento gástrico da doença de Crohn, e podem refletir um defeito subjacente na imunidade inata. Estas características, no entanto, são também descritas em pacientes com infecção por *Helicobacter pylori*. O papel destas anormalidades gástricas no diagnóstico da doença de Crohn foi avaliada em uma população com alta prevalência de infecção por *H. pylori*. ***Métodos*** – Trinta e sete pacientes com doença de Crohn, 26 pacientes com colite ulcerativa e 30 pacientes-controle foram incluídos. O status de infecção por *H. pylori* foi avaliado pelo teste da urease e histologia. A presença de gastrite focal e microagregados de macrófagos foi avaliada. ***Resultados*** - Gastrite focal estava presente em 24% dos pacientes com doença de Crohn, 4% dos indivíduos com colite ulcerativa e 11,5% dos controles, apresentando uma sensibilidade e especificidade para doença de Crohn de 24% e 88%, respectivamente. Microagregados de macrófagos foram encontrados em todos os grupos, mas foram apenas detectados em colite ulcerativa e controles em associação com infecção por *H. pylori*, com sensibilidade e especificidade para doença de Crohn de 61% e 69%, respectivamente. Na ausência da infecção por *H. pylori* comprovada, gastrite focal e microagregados de macrófagos foram significativamente associados com doença de Crohn ($P<0,02$ e $P = 0,001$, respectivamente). ***Conclusões*** - Gastrite focal e microagregados de macrófagos são sugestivos de doença de Crohn apenas em pacientes com avaliação dignóstica negativa para *H. pylori*.

DESCRITORES - Doença de Crohn. Colite ulcerativa. Gastrite. Macrofagos. *Helicobacter pylori*.

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