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ORIGINAL ARTICLE

Retrospective Study

Microscopic colitis in patients with mild duodenal damage: A new clinical and pathological entity ("lymphocytic enterocolitis")?

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Abstract

AIM

To evaluate the potential association between mild duodenal damage and microscopic colitis (MC).

METHODS

We retrospectively included 105 consecutive patients with type I Marsh-Oberhuber duodenal damage and negativity for immunoglobulin A anti-endomysium and anti-tissue transglutaminase. The following parameters were analyzed: Sex, age at execution of esophago-gastroduodenoscopy, duodenal damage, and number of intraepithelial lymphocytes at biopsies, prevalence

of *Helicobacter pylori* infection, age at execution of colonoscopy, macroscopic and microscopic features of colonoscopy, family history of gastrointestinal and autoimmune diseases, smoking habits, biochemical parameters of inflammation and autoimmunity, use of proton pump inhibitors or nonsteroidal anti-inflammatory drugs, adverse reactions to drugs or foods, pathologies known to be associated with celiac disease or MC, living on a gluten-free diet or on a gluten-low diet for at least 1 mo.

RESULTS

Colonoscopy was performed in 59 patients, but only in 48 of them biopsies were taken in the entire colon. Considering the latter cohort, the diagnosis of MC was met in 25 (52.1%) patients while in 18 patients other pathologic findings were reported: 13 (27%) cases of nonspecific inflammatory bowel disease, 2 (4.2%) cases of Crohn's disease, 2 (4.2%) cases of eosinophilic gastroenteritis, and 1 (2.1%) case of autoimmune enteritis. Five (10.4%) patients had a normal colonoscopic result. Matching the groups by age, and considering only patients who underwent colonoscopy (42.7 ± 15.5 years) *vs* those who did not undergo colonoscopy (36.9 ± 10.6 years), a statistical difference was found (P = 0.039). Focusing on symptoms, diarrhea was statistically more prevalent in MC group than in patients who did not undergo colonoscopy (P = 0.03).

CONCLUSION

Mild duodenal damage is associated with MC in more than half of the cases. This association supports the hypothesis of a link between these two entities.

Key words: Autoimmune diseases; Celiac disease; *Helicobacter pylori*; Intraepithelial lymphocytes; Lymphocytic colitis; Lymphocytic enterocolitis; Microscopic colitis

Core tip: Scarce information is available on patients with symptoms suggestive for celiac disease but with negative serologic tests and mild duodenal damage (type I Marsh-Oberhuber classification). Our data show that mild duodenal damage is associated with microscopic colitis in more than the half of the investigated cases. This association may support the hypothesis of a new clinical and pathological entity, the "lymphocytic enterocolitis".

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disease characterized by a pathological reaction against gluten proteins[1]. Currently, the prevalence of CD in the general population is proximally 1%, with a ratio between diagnosed and undiagnosed cases of about 1:7[2,3]. CD presents often signs and symptoms such as chronic diarrhea, bloating, abdominal pain and malabsorption[4]. However, in a substantial number of cases, CD can manifest only extra-intestinal symptoms or signs, and it can be associated with autoimmune pathologies, as autoimmune thyroiditis, type I diabetes mellitus and rheumatoid arthritis[5,6]. The diagnosis of CD is based on the finding of positive antibody tests (anti-endomysium and anti-tissue transglutaminase), confirmed by biopsies taken during esophagogastroduodenoscopy (EGD) that reveal the characteristic duodenal damage. The Marsh-Oberhuber classification is usually used to grade the severity of duodenal lesions, with the type III representative of CD[7]. The search for human leukocyte antigen (HLA) haplotypes DQ2 and DQ8, due to its high negative predictive value, is used to exclude CD[8]. Nevertheless, there are patients with suggestive symptoms of CD, mild duodenal damage [*i.e.*, an increase of intraepithelial lymphocytes (IEL)] defined type I, according to Marsh-Oberhuber classification, and negative antibody tests. This clinical condition, that does not conform with the diagnosis of CD, needs to be investigated for other causes[9].

Microscopic colitis (MC) is a chronic inflammatory bowel disease, distinct in lymphocytic colitis (LC)[10] and collagenous colitis (CC)[11]. The diagnosis of MC is obtained by multiple colonic mucosal biopsies taken during colonoscopy[12]. Typically, in CC, the histological feature is a thickening of the subepithelial collagen layer beneath the basal membrane, of more than 7-10 μm (0-3 μm in the normal colon)[13]. The histological feature of LC is the presence of more than 20 IEL/100 surface epithelial cells (< 5 IEL/100 in the normal colon)[14]. Paucicellular LC is a term used when the number of IEL is comprised between 5 IEL/100 and 20/100 surface epithelial cells. In MC, IEL are T-Lymphocyte $CD3^+$ and $CD8^+$, similar to those described in case of type I Marsh-Oberhuber lesions. Previously considered rare, MC is now a relatively common cause of chronic watery nonbloody diarrhea, especially in the elderly[15]. Both LC and CC are associated with autoimmune diseases and allergy[16]. Finally, it has been shown that patients with MC have an increased rate of HLA-DQ2 and HLA-DQ8 positivity[17], even if this association is less strict than with CD.

Although some authors reported an association between MC and type I Marsh-Oberhuber duodenal damage[18-23], the interpretation of this finding is poorly described. Nevertheless, there are few studies[24] that searched for the inverse association.

The aim of this study was to evaluate, for the first time, the association between type I Marsh-Oberhuber

duodenal damage and MC, arguing for the existence of a possible "microscopic enterocolitis"[25,26].

MATERIALS AND METHODS

We retrospectively included 105 (86 females, mean age 40.1 ± 13.7) consecutive patients with type Ⅰ Marsh-Oberhuber duodenal damage and negativity for anti-endomysium (EmA) and anti-tissue transglutaminase (tTG) immunoglobulin (Ig)A antibodies. No sign of Whipple disease were reported in duodenal biopsies. Patients affected by small bowel bacterial overgrowth were excluded from the analysis. The analysis included patients observed in the period 1 January 2003-31 December 2013 in the outpatients clinic of the Unit of Gastroenterology and Hepatology, Molinette Hospital, Turin, Italy.

In 5 cases of IgA deficiency, the genetic assessment (HLA-DQ2/DQ8) was performed: In 3, the result was negative while in the remaining 2 HLA-DQ2 positivity was found.

The following parameters were analyzed: Sex, age at execution of EGD, duodenal damage with number of IEL at biopsies, age at execution of colonoscopy, macroscopic and microscopic features of colonoscopy, family history of gastrointestinal and autoimmune diseases, smoking habits, dosage of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and anti-nuclear antibody (ANA), use of proton pump inhibitors (PPIs) or nonsteroidal anti-inflammatory drugs (NSAIDs)[27], adverse reactions to drugs or foods, pathologies associated with CD or MC, living on a gluten-free diet or on a gluten-low diet for at least 1 mo. Data on the prevalence of watery diarrhea, constipation, epigastric pain, abdominal pain, weight loss, nausea and/or vomiting, bloating, and asthenia were collected. Malabsorption was defined as the presence of at least one of these elements: Hemoglobin (Hb) < 12 g/L and low levels of serum iron or folate or vitamin B12; hypoalbuminemia; weight loss > 10% without hypocaloric diet. *Helicobacter pylori* (*H. pylori*) infection was investigated by urea breath test and gastric biopsies. The previous eradication treatment of this infection, if any, was reported.

The pharmacological anamnesis for assumption of prednisone, mesalamine, salazopyrin, budesonide, and antibiotics (rifaximin, ciprofloxacin, metronidazole) was conducted. Patients who took serotonin reuptake inhibitors or antiplatelets were excluded from the analysis.

Statistical analysis

For parametric data, we initially used the "normal probability plot", to value a normal data distribution; in case of positive return, the Student T test to match the two subgroups was used.

For non-parametric data, the subgroups were matched with the Yates' χ^2 test or with the Fisher's exact test if data were $\leqslant$ 5.

Confidence interval (CI) was set at 95%, with the statistical significance set at P value < 0.05. All statistical analyses were performed using MedCalc software (MedCalc Software, version 9.2.1.0).

RESULTS

Overall, colonoscopy was performed in 59 patients, but in only 48 cases biopsies were taken along the entire colon. In the remaining 11 cases, biopsies were not taken or taken only in the left colon. The histological findings permitted to divide the cohort into two groups: That including 25 patients with diagnosis of MC and that including 23 patients without MC (Figure 1).

Matching by age, patients who underwent colonoscopy (42.7 ± 15.5 years) *vs* those who did not undergo colonoscopy (36.9 ± 10.6 years), a statistical difference was found (P = 0.039). On the contrary, there was no significant difference between the group of patients who did not undergo colonoscopy (36.9 ± 10.6 years) *vs* the group who underwent colonoscopy and executed multiple biopsies (40.4 ± 13.7 years) (P = 0.186). Considering the symptoms, there were no statistical differences between patients who did not undergo colonoscopy *vs* those who underwent colonoscopy and executed multiple biopsies (P = 0.09 and P = 0.14 for epigastric pain and diarrhea, respectively). Diarrhea was statistically more prevalent in MC group than in patients who did not undergo colonoscopy (P = 0.03). Patients who did not undergo colonoscopy *vs* those who underwent colonoscopy and executed multiple biopsies had not statistical differences when comparing the heterodimers HLA-DQ2 and HLA-DQ8 (P = 0.19).

Among patients who underwent colonoscopy, an inflammatory pattern was found in 89.6% of cases. Focusing on the 25 patients with MC, the females to males ratio resulted 5:1 and the mean age was 40 ± 16.3 years. The diagnosis was LC in 13 cases, paucicellular LC in 9, CC in 2, and undefined MC in the remaining patient. The average duodenal IEL were 41.6/100 epithelial cells and colonic IELs were 25.4/100 epithelial cells. Watery diarrhea was present in 17/25 (68%) patients, abdominal pain in 16/25 (64%), weight loss in 11/25 (44%), nausea or vomiting in 7/25 (28%), epigastric pain in 6/25 (24%), asthenia in 5/25 (20%), bloating in 4/25 (16%), and gastroesophageal reflux disease (GERD) in 2/25 (8%). A family history of Crohn's disease, thyroiditis, rheumatoid arthritis or spondylitis, was present in 1/25 (4%) patient for each one. Regarding smoking habits, 19/25 (76%) patients were non-smokers while the remaining 6 (24%) were smokers. ANA test resulted positive in 4/25 (16%) patients, ESR increased in 2/25 (8%), and CRP in 2/25 (8%). Four out of twenty-five (16%) patients had a positive history of PPIs use, and 1/25 (4%) of NSAIDs use. Autoimmune thyroiditis was diagnosed in 4/25 (16%) patients, asthma in 3/25 (12%), rheumatoid arthritis in 3/25 (12%). Anamnesis of adverse reactions to drugs or foods resulted in 10/25 (40%) patients.

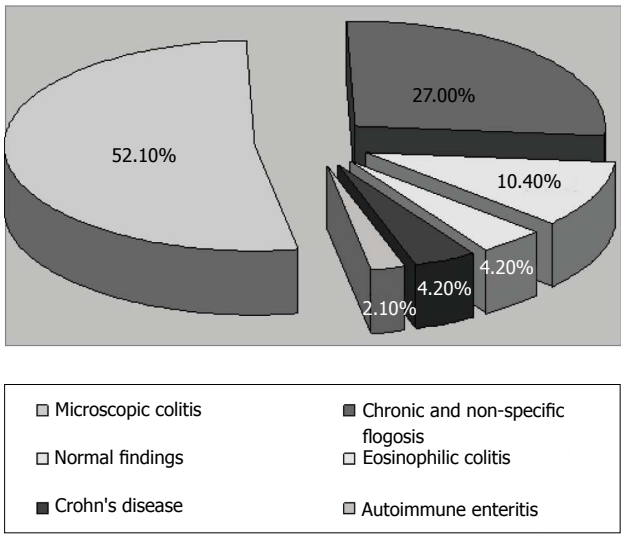

Figure 1 Microscopic findings at colonoscopy (48 cases).

Table 1 Main clinical and laboratory parameters of enrolled patients

	Patients with MC	Patients without MC	*P* value
Watery diarrhea	17/25 (68%)	10/23 (43%)	0.08
Abdominal pain	16/25 (64%)	10/23 (43%)	0.15
Weight loss	11/25 (44%)	3/23 (13%)	0.01
Nausea/vomiting	7/25 (28%)	4/23 (17%)	0.29
Epigastric pain	6/25 (24%)	5/23 (21%)	0.85
Asthenia	5/25 (20%)	4/23 (17%)	0.55
Bloating	4/25 (16%)	5/23 (21%)	0.44
GERD	2/25 (8%)	4/23 (17%)	0.33
Constipation	0/25 (0%)	4/23 (17%)	0.04
History of allergy	10/25 (40%)	10/23 (43%)	0.40
PPIs use	4/25 (16%)	6/23 (26%)	0.44
NSAIDs use	1/25 (4%)	0/23 (0%)	0.34
ANA positivity	4/25 (16%)	8/23 (34%)	0.46
ESR increased	2/25 (8%)	6/23 (26%)	0.13
CRP increased	2/25 (8%)	5/23 (21%)	0.21
Helicobacter pylori infection	6/25 (24%)	8/23 (34%)	0.61

MC: Microscopic colitis; GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors; NSAIDs: Nonsteroidal anti-inflammatory drugs; ANA: Anti-nuclear antibody; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

Thirteen patients (52%) had HLA-DQ2 positivity, 8 (32%) HLA-DQ2/DQ8 negativity, and 4 (16%) HLA-DQ8 positivity. Regarding *H. pylori* infection, 19/25 (76%) had negativity *ab initio* while 4 out of 6 with positivity (66.6%), eradicated the infection after antibiotic treatment. None of the tested patients had positivity at coproculture or at parasitological fecal test (6 and 2 cases, respectively). Fourteen (56%) patients undertook a gluten-free diet for at least 1 mo with a clinical improvement in 3/14 (21.4%). Malabsorption was observed in 12 (48%) patients.

Among patients without MC, the female to male ratio resulted 3.8:1 and the mean age was 40.5 ± 13.7 years. The diagnosis was of chronic and non-specific inflammation in 13 (56.5%) cases, there was a normal finding in 5 (21.7%), eosinophilic colitis in 2 (8.6%), Crohn's disease in 2 (8.6%), and autoimmune enteritis in the last one (4.3%). The average duodenal IEL resulted 42.1/100 epithelial cells. Based on the available data, a family history of Crohn's disease, rheumatoid arthritis or spondylitis was reported in one out of 23 (4.3%) patients for each disease. Regarding smoking habits, 15/23 (65.2%) patients were non-smokers while the remaining 8 (34.8%) were smokers. Abdominal pain was present in 10/23 (43.4%) patients, watery diarrhea in 10/23 (43.4%), epigastric pain in 5/23 (21.7%), bloating in 5/23 (21.7%), asthenia in 4/23 (17.3%), nausea or vomiting in 4/23 (17.3%), GERD in 4/23 (17.3%), constipation in 4/23 (17.3%), and weight loss in 3/23 (13.0%). ANA test resulted positive in 8/23 (34.8%) patients, ESR and CPR was increased in 6/23 (26.1%) and 5/23 (21.7%), respectively. A history of PPIs or NSAIDs use was reported in 6/23 (26.1%) and no patient, respectively. Autoimmune thyroiditis was reported in 3/23 (13%) of the patients, asthma in 2/23 (8.6%), rheumatoid arthritis in 2/23 (8.6%), systemic erythematosus lupus (SLE), autoimmune hepatitis and multiple autoimmune diseases in 1/23 (4.3%) for each one. Adverse reactions to drugs or foods resulted in 10/23 (43.4%) patients. Ten (43.4%) patients had HLA-DQ2/DQ8 negativity, 9 (39.1%) had HLA-DQ2 positivity, 3 (13%) HLA-DQ8 positivity, and one (4.3%) had HLA-DQ2/DQ8 positivity. Regarding *H. pylori* infection, 15/23 (65.2%) of the tested patients were negative *ab initio*, while 8/23 (34.8%) were positive. Of the latter group, 5 out of 8 (62.5%) eradicated the infection after antibiotic treatment. None of the tested patients had positivity at coproculture or at parasitological fecal test (4 and 1 case, respectively).

Comparing patients with MC *vs* those without MC (Table 1), the only variables that had a statistical difference were weight loss ($P = 0.01$), more frequent in case of MC, and constipation ($P = 0.04$) more frequent in absence of MC. Diarrhea ($P = 0.08$), abdominal pain ($P = 0.15$), epigastric pain ($P = 0.85$), GERD ($P = 0.33$), autoimmune thyroiditis ($P = 0.79$), smoking habits ($P = 0.66$), asthma ($P = 0.72$), rheumatoid arthritis ($P = 0.72$), autoimmune hepatitis ($P = 0.31$), multiple autoimmune diseases ($P = 0.35$), HLA-DQ2 positivity ($P = 0.51$), HLA-DQ8 positivity ($P = 0.79$) did not reach statistical significance.

Among patients suffering from MC, budesonide was used in 14 patients, of whom 13 (92.9%) responded to therapy; 8 patients used mesalamine, of them 4 (50%) responded to therapy; 4 patients used salazopyrin, with response in 2 (50%); 1 patient used prednisone, with response. No difference about the response to therapy resulted from the comparison between budesonide and mesalamine ($P = 0.27$), budesonide and salazopyrin ($P = 0.41$), budesonide and prednisone ($P = 0.94$). Among patients without MC, 7 used budesonide and 6/7 (85.7%) responded to therapy; 4 patients used prednisone without response; 6 patients used mesalamine with response in 3 (50%).

DISCUSSION

In this study, we found a strong association between type Ⅰ Marsh-Oberhuber duodenal damage and MC, mainly LC. More than half (52.1%) of the patients who underwent colonoscopy with multiple biopsies had MC. This percentage is significantly higher than the historical prevalence of MC in the general population (0.5%)[28]. An intriguing data was that LC and paucicellular LC, considered together, were diagnosed in much more cases than CC (22 *vs* 2, respectively). Usually, literature considered incidence and prevalence of CC higher than LC; however, more recent studies, according to our data, report that the incidence of LC is significantly rising[29].

Patients who underwent colonoscopy were significantly older than those who did not undergo colonoscopy. This could be partially explained considering the age as a parameter associated to augmented risk of malignancy. Hence, clinicians recurred to endoscopy in case of unexplained symptoms and increasing age. However, there was no difference in the median age between patients who did not undergo colonoscopy *vs* those who underwent colonoscopy with multiple biopsies.

Considering biochemical results and symptoms among various groups, only chronic diarrhea was significantly higher in patients with MC than in those who did not undergo colonoscopy (P = 0.03). Thus, in patients with mild duodenal damage only this symptom could predict MC. However, due to its multifactorial pathogenesis, the presence of diarrhea cannot be the only element to decide whether this type of patients should undergo colonoscopy with multiple biopsies. On the other hand, the absence of diarrhea cannot exclude the indication for colonoscopy with multiple biopsies, because only 5 out of 48 (10.4%) patients who had a colonoscopy with biopsies had normal microscopic findings, despite suffering also from abdominal pain, weight loss, constipation, positive fecal occult blood. The search for HLA-DQ2/DQ8 haplotypes seems to be useful, although the data in our retrospective study are not broad enough to provide definitive conclusions. Since this test has a very high negative predictive value in the diagnosis of CD, in patients with mild duodenal damage, negative serological tests for CD and the above reported symptoms, the negativity of HLA-DQ2/DQ8 haplotypes can definitively exclude this disease and propel to search for other etiologies, as MC.

The median age at which the diagnosis of MC was made in our patients (40 years) is lower than literature reports. Such finding may contrast with the idea of MC as disease of the elderly pointing out to a possible underestimation of this condition.

Another element that emerged from this study was the low prevalence of *H. pylori*-infection both in patients with MC (24%) than without MC (34%). The literature reports that *H. pylori* infection is related to duodenal lymphocytosis[9], which disappears after bacterial eradication. At the same time, we have recently found an inverse association between MC and *H. pylori* infection[29]. The results of the present study agree with the fact that in case of mild duodenal damage and MC the prevalence of *H. pylori* infection is lower than the general population (in our case 24% *vs* 47%)[30]. Moreover, the rate of *H. pylori* eradication in this context, is similar to that obtained in the general population[31].

In our study, the role of pharmacological therapy in the pathogenesis of MC is not fully clear. In fact, only 4 patients used PPIs and 1 patient used NSAIDs before the diagnosis of MC. This differs from the well-known data reporting that this type of medications are often implicated as a cause of MC[32], and could be explained by a β error (*i.e.,* the failure to detect an effect that is present) due to the small sample size. Considering the outcome of therapy used to treat MC, budesonide emerged as the best treatment, due to a clinical improvement, in more than 90% of patients. Mesalamine seemed to be a valid therapeutic approach for less severe cases. According to some reports, our results confirm the appropriateness of this management[32].

Although in literature an association between MC and malabsorption is not reported[33], in our study 12 (48%) patients presented signs of it. A potential disease of the small intestine, beyond the duodenum, could explain these features. More efforts are thus needed to understand this clinical condition.

This retrospective analysis shows inadequate habits of clinicians to search for a coproculture or a parasitological test; also the search for *Giardia Lamblia* was out of routine. Such investigations should play an important role in the attempt to identify the cause of duodenal damage. In fact, literature reports that the search for *Giardia Lamblia* or other pathogens should be included in the diagnostic work up of type Ⅰ Marsh-Oberhuber duodenal damage[34].

A potential limitation of our study is its retrospective design with a theoretical loss of balance on parameters analyzed. Nevertheless, we noticed uniform diagnostic and follow-up criteria.

In conclusion, MC is frequently associated with mild duodenal damage. This association may suggest the existence of a "microscopic enterocolitis", and specifically of a "lymphocytic enterocolitis", that involves the entire gastrointestinal tract. It is advisable to perform a colonoscopy with biopsies in all patients with type Ⅰ Marsh-Oberhuber duodenal damage and symptoms as chronic diarrhea, abdominal or epigastric pain, loss of weight, after exclusion of standard causes.

COMMENTS

Background

The diagnosis of celiac disease (CD) is based on the finding of positive antibody tests (anti-endomysium and anti-tissue transglutaminase), confirmed by biopsies that reveal the characteristic duodenal damage. The Marsh-Oberhuber classification is usually used to grade the severity of duodenal lesions, with the type Ⅲ representative of CD. Nevertheless, there are patients with suggestive symptoms of CD, mild duodenal damage [*i.e.,* an increase of intraepithelial lymphocytes (IEL)] defined type Ⅰ, according to Marsh-Oberhuber classification,

and negative antibody tests. This clinical condition, that does not conform with the diagnosis of CD, needs to be investigated for other causes as well as for comorbidities. Microscopic colitis (MC), previously considered rare, was demonstrated as a relatively common cause of chronic, watery, diarrhoea. While some isolated studies reported some association between MC and Marsh I duodenal damage, the interpretation of this finding is poorly described.

Research frontiers

To date, scarce information is available on the association between mild duodenal damage and MC.

Innovations and breakthroughs

This study is the first showing that type I Marsh-Oberhuber duodenal damage is strongly associated with MC, mainly lymphocytic colitis (LC). More than half (52.1%) of the patients who underwent colonoscopy with multiple biopsies had MC. This percentage is significantly higher than prevalence of MC in the general population (0.5%). This association supports the hypothesis of a link between these two entities.

Applications

These findings, of association between type I Marsh-Oberhuber duodenal damage and MC, may suggest the existence of a "microscopic enterocolitis", and specifically of a "lymphocytic enterocolitis", that involves the entire gastrointestinal tract. It is advisable to perform a colonoscopy with biopsies in all patients with type I Marsh-Oberhuber duodenal damage and symptoms as chronic diarrhea, abdominal or epigastric pain, loss of weight, after exclusion of standard causes.

Terminology

The Marsh-Oberhuber classification is usually used to grade the severity of duodenal lesions, with the type III representative of CD. There are patients with suggestive symptoms of CD, mild duodenal damage (*i.e.*, an increase of IEL) defined type I, according to Marsh-Oberhuber classification, and negative antibody tests, that do not conform with the diagnosis of CD. MC is a chronic inflammatory bowel disease, distinct in LC and collagenous colitis. The histological feature of LC is the presence of more than 20 IEL/100 surface epithelial cells (< 5 IEL/100 in the normal colon). Paucicellular LC is a term used when the number of IEL is comprised between 5 IEL/100 and 20/100 surface epithelial cells. In MC, IEL are T-Lymphocyte $CD3^+$ and $CD8^+$, similar to those described in case of type I Marsh-Oberhuber lesions. Here we report for the first time the association between type I Marsh-Oberhuber duodenal damage and MC, arguing for the existence of a possible "microscopic enterocolitis".

Peer-review

This is an interesting manuscript.

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