

# A practical approach to histopathologic diagnosis of microscopic colitis

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## Abstract

Lymphocytic colitis and collagenous colitis are two histologic forms of microscopic colitis, a condition which was first recognized over 30 years ago. It is often found in adults with chronic, watery diarrhea although endoscopic examination of the colon is frequently normal. The diagnosis is based on microscopic examination of colonic biopsies. The aim of this review is to familiarize general surgical pathologists with the morphologic features of lymphocytic and collagenous colitis. In addition, this review emphasizes good communication with the endoscopist to allow correct recognition and ensure appropriate treatment.

## Keywords

Colitis, microscopic colitis, collagenous colitis, lymphocytic colitis.

## INTRODUCTION

Microscopic colitis (MC) is a term used to describe a medical condition characterized by chronic watery diarrhea but with an almost normal endoscopic appearance of the mucosa of the colon and typical histopathological changes. (1) Two histological types of MC have been described: lymphocytic colitis (LC) and collagenous colitis (CC). Each has its own epidemiology and associated diseases but both follow similar clinical course. In addition, they share similar histological features such as inflammatory cells and damage to the superficial epithelium.

The term microscopic colitis has been used since 1980. (1) At that time its incidence was very low, but recent literature shows an increasing number of MC cases which now account for between 9.5% and 10.2% of the patients with chronic watery diarrhea who have undergone endoscopy and have had biopsies. (2, 3)

The etiologies and pathogenesis of LC and CC are not yet very clear. However, observational investigations suggest an association between MC and several autoimmune diseases

such as autoimmune thyroiditis, rheumatoid arthritis, celiac disease, and other diseases such as Intestinal Inflammatory Disease (IBD). (4-6) Use of medicines including NSAIDs, (7) proton pump inhibitors, (8) and histamine receptor inhibitors (ranitidine and cimetidine) (9,10) have been associated with both LC and CC.

Colon biopsies are essential in the diagnosis of MC. In general, recognition of typical forms of LC and CC can be achieved in most cases, and there are excellent rate of inter observer and intra agreements among pathologists trained in gastrointestinal pathology. (11) Nevertheless, the less typical forms are difficult to recognize. The aims of this review are to familiarize pathologists who do not have specific gastrointestinal training with the morphologies of LC and CC, to suggest standardization of reports, and to highlight the importance of good communication with the endoscopist for correct diagnosis of these entities.

This article is based on a review of original and review articles on the topic published in English and Spanish in indexed journals from the PubMed and SciELO databases with the addition of personal contributions from the

authors. Keywords used in both English and Spanish were “Colitis”, “microscopic colitis”, “lymphocytic colitis” and “collagenous colitis”.

## LYMPHOCYTIC COLITIS

### Epidemiology

The annual incidence of LC in Europe ranges from 1.1/100,000 people to 3.1/100,000 people with a prevalence ranging from 10/100,000 to 15.7/100,000 people. (2) In North America, the incidence is 5.5/100,000 people with a prevalence of 63.7/100,000 people at the end of 2001. (12) In Latin America, isolated figures for the prevalence of MC exist for countries like Uruguay, (13) but we found no publications on the epidemiology of MC in Colombia. The average age of patients at diagnosis is 60.7 years: MC is up to 2.7 times more common among women than men. (14)

### Symptoms

Patients with LC present chronic watery diarrhea with an average duration before diagnosis of three and a half month. They have between four and six fecal depositions per day. (15) Other symptoms like abdominal pain, incontinence, urgency, flatulence and weight loss have also been associated with LC. (3, 16)

### Endoscopic findings

The mucosae of the majority of patients have standard endoscopic appearances. A small proportion may have erythema, edema and an abnormal distribution pattern of vessels. (17) Changes in LC may be irregular in their distribution in the different portions of the colon, but are sometimes more severe in the right colon. (18) It is recommended that biopsies be taken from the ascending colon, the transverse colon, the descending colon and the rectosigmoid colon and that each biopsy be place in a separate container. (19)

### Histological findings

LC is characterized by an increased proportion of intraepithelial lymphocytes (IEL) (more than 20 lymphocytes/100 epithelial cells) in the superficial epithelium and in the epithelium of the crypts. (20) The mucosa has a standard architectural pattern accompanied by damage to the superficial epithelium and a mixed mononuclear inflammatory infiltrate (plasma cells, lymphocytes) with few eosinophils in the lamina propria and absence of sub-

epithelial collagen deposits (Figure 1). (21) The damage to the superficial epithelium is associated with infiltration of lymphocytes and with degenerative characteristics such as cytoplasmic vacuoles, loss of mucin, and irregularities of the cell nuclei including pyknosis and flattening. (20)

The IEL have small circular nuclei and are generally surrounded by a clear halo. (Figure 2) Intraepithelial lymphocytosis is evident, but since most pathologists have a good idea of the normal pattern of distribution of the inflammatory cells in the colonic mucosa there is usually no need for a cell count. However, when there is any doubt about whether the number of IELs has increased, a lymphocyte count should be done. It is necessary to note that increased numbers of IELs is a normal finding for superficial epithelium overlying lymphoid aggregates and should not be interpreted as a LC. Consequently, in the context of MC, IEL counts are not recommended in those areas. (18)

The use of immunohistochemical techniques is not of vital importance for the diagnosis of LC because diagnosis can be done with routine hematoxylin-eosin (HE) staining. However, there are reports that conclude that in the appropriate clinical setting, the use of CD3 may have additional value for diagnosis of LC. (22)

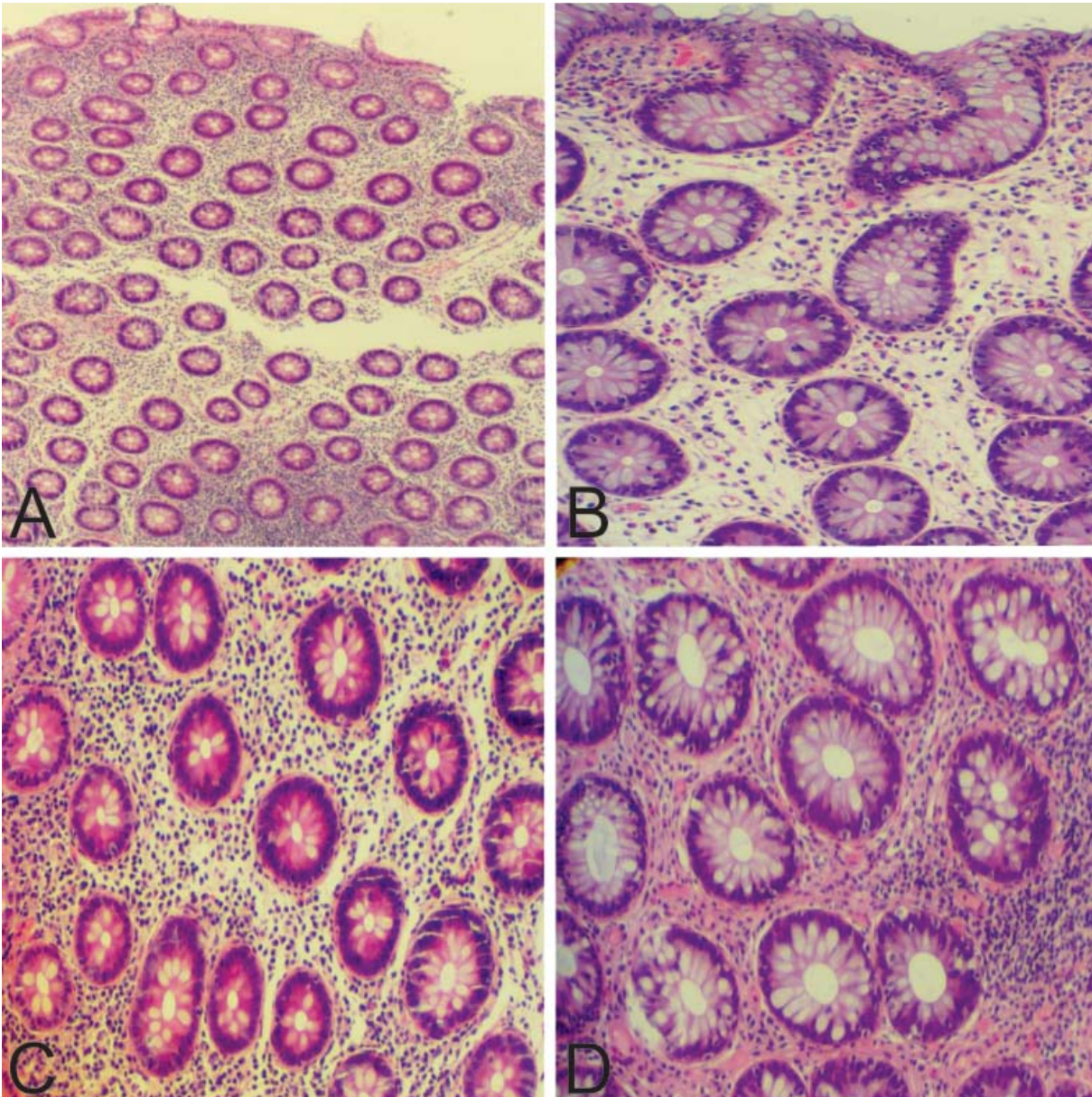
In the literature two variants of histopathological LC have been described, although there are very few reported cases in both variants, moreover they are without apparent prognostic significance for patients. The first is paucicellular LC which has been described as having symptoms similar to those already discussed but which histologically has raised foci, slightly elevated levels of IEL and lymphoplasmacytic infiltrate in the lamina propria separated by fragments of normal mucosa. (23) The second variant is LC with giant cells. This refers to the presence of giant subepithelial cells in the context of typical LC. (24)

### Differential diagnosis

Among the most common entities requiring differential diagnosis from LC are resolved acute active colitis, collagenous colitis, inflammatory bowel disease (IBD) and enteropathy associated with T-cells lymphoma. The presence of neutrophils indicates acute colitis which allows us to differentiate between LC, active self-limited colitis in the process of resolving itself, and active colitis overlapping with LC (Figure 3).

Both entities have increased IEL levels, but patients may be more motivated to see a doctor when chronic diarrhea has recently worsened (active infectious overlapped colitis). In cases in which this pattern of inflammation is present, and in the appropriate clinical context, it is recommended that the diagnosis be made in a descriptive way that indicates to the attending physician that this may be





**Figure 1.** Histological features of lymphocytic colitis. A, B, C and D, increased amounts of mononuclear inflammatory infiltrate in the lamina propria, intraepithelial lymphocytosis and architectural pattern of conserved crypts. (hematoxylin-eosin, 4x (A), 10x (B, C, D)).

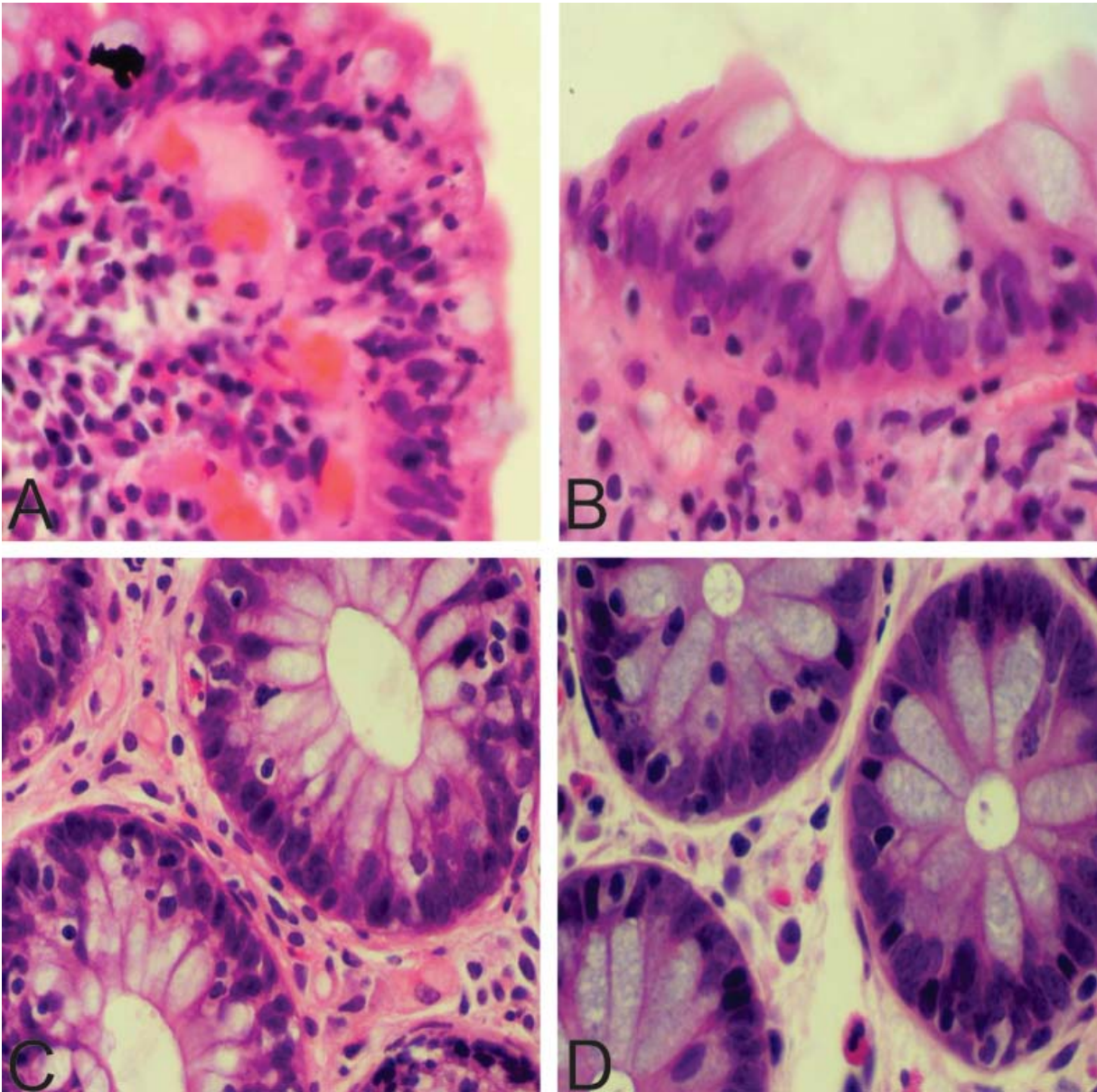
a case of LC and overlapping active colitis or it may be the resolution phase of self-limited colitis (Table 1). If symptoms persist, repetition of the colonoscopy/biopsy in two to three months can be considered in order to establish a definitive diagnosis.

An accurate assessment of the subepithelial collagen band helps differentiate between LC and colon cancer. However, in cases with borderline features a Masson trichrome stain may be helpful (see below). Differentiating between LC and IBD is simple because in cases of IBD the architecture of the crypts is abnormal. However, it can be difficult in the context

of LC with IBD because of focal features or because of true coexistence of the two conditions which has also been reported. The overall assessment of the endoscopic and clinical contexts and the predominant lesion pattern shown in the biopsies help differentiate between these two entities. (25)

Intraepithelial lymphocytosis associated with T cell lymphoma is strongly linked to celiac disease and primarily involves the small intestine. Nevertheless, it can also affect the colon. Histologically, an infiltration of atypical small lymphocytes is observed occupying the intestine wall. In most cases these lymphocytes present the following immu-





**Figure 2.** Histological features of lymphocytic colitis. A, B, C and D. Damage to the superficial epithelium, superficial intraepithelial lymphocytosis in the crypts and intraepithelial lymphocytes surrounded by a white halo. (Hematoxylin-eosin, 10x (A), 40x (B, C, D)).

nohistochemical profile: CD45 (+), CD3 (+), CD7 (+) CD4 (-), CD8 (-), TIA-1 (+), granzyme B (+) perforin (+) and clonal rearrangements of TCR  $\beta$  and  $\gamma$  (26).

## COLLAGENOUS COLITIS

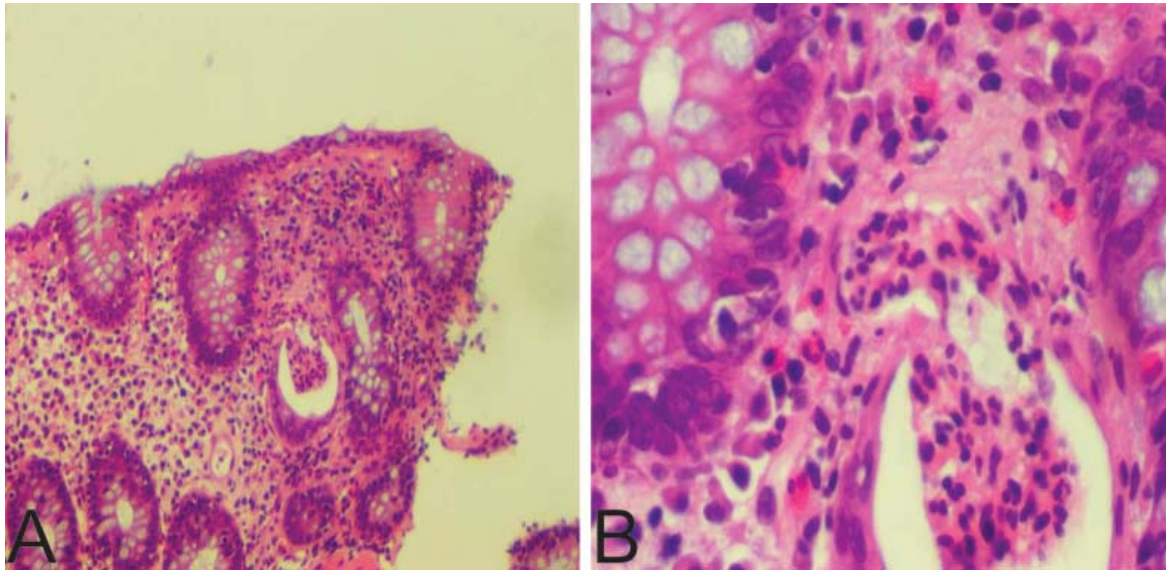
### Epidemiology

The annual incidence of CC in Europe ranges from 0.6/100,000 people to 5.2/100,000 people, while its prevalence ranges from 10/100,000 people to 15.7/100,000

people. (2). In the United States the annual incidence was 3.1/100,000 people and the prevalence was 39.3/100,000 people at the end of 2001. (12) The average age of patients at diagnosis is 63 years old with a range between 29 and 93 years old. (14) It is quite unusual among children (27) and it is three times more common in women than in men. (14)

### Symptoms

Patients with CC present symptoms similar to those of LC, in particular they have chronic watery diarrhea which



**Figure 3.** Histological characteristics of acute colitis. A, B, C, D damage to the superficial epithelium, intraepithelial lymphocytosis and lymphocytosis in the epithelial crypts, cryptitis and increases of the inflammatory infiltrate in the lamina propria with abundant neutrophils. (Hematoxylin-eosin, 4x (A, B), 40x (C, D)).

**Table 1.** Characteristics of Lymphocytic Colitis and Collagenous Colitis

| Characteristics       | Lymphocytic Colitis   | Collagenous Colitis   |
|-----------------------|---|---|
| Average age           | 60.7 years;   | 63 years  |
| male: female ratio    | 1:2.7   | 1:3   |
| Symptoms              | Chronic watery diarrhea with average duration between 3 and 30 months.<br>Number of daily fecal depositions between 4 and 6.  | Chronic watery diarrhea with average duration of 24 months.<br>Number of daily fecal depositions, 6.  |
| Endoscopic findings   | Mucosa of normal appearance. Small amounts of erythema, edema and abnormal distribution vessels pattern may be present.   | Mucosa of normal appearance. However, findings of mucosal vascular pattern disturbances, nodularity and perforation during or after colonoscopy have been reported.   |
| Histological findings | Mucosa with normal architectural pattern.<br>Increased proportion of IEL (>20 lymphocytes/100 epithelial cells) in the superficial epithelium and in the crypts.<br>Damage to the superficial epithelium.<br>Increase of the inflammatory infiltrate in the lamina propria. | Mucosa with normal architectural pattern.<br>Thickened subepithelial collagen band (>10 µm thick).<br>Increased proportion of IEL.<br>Damage to the superficial epithelium with detachment and separation of the basal membrane. Increases of inflammatory infiltrate in the lamina propria with excess of eosinophils in some cases. |

IEL: intraepithelial lymphocytes.

lasts an average of 24 months before diagnosis. The average number of fecal depositions per day is six. (14)

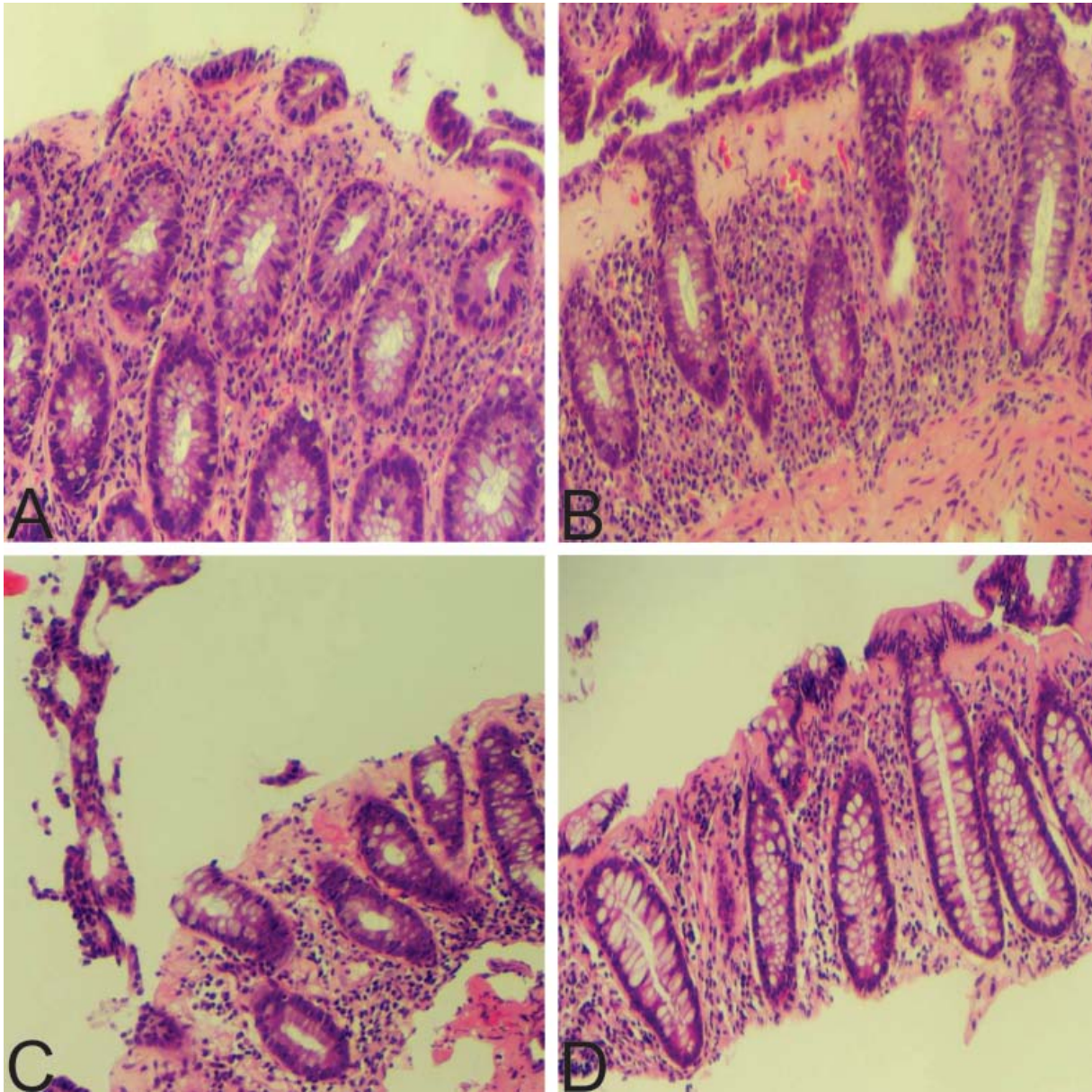
### Endoscopic findings

Although the mucosae of most patients with CC appear normal, findings such as altered mucosal vascular patterns and nodularity have been reported. Also, there have been cases of perforation which occurred during colonoscopy

but were reported 1 to 5 days after the procedure was performed. (17, 28)

As in LC, alterations occurring in CC may be distributed irregularly, but are most common in the proximal colon. (17) However, since CC does not compromise only the right colon, (19) it is recommended that multiple biopsies of the mucosa be taken, including from the right colon, the transverse colon, the descending colon and the rectosigmoid colon. It is preferable to send them to the laboratory in separate containers. (19)





**Figure 4.** Histological features of collagenous colitis. A, B and D, increases of mononuclear inflammatory infiltrate in the lamina propria with eosinophils, intraepithelial lymphocytosis, preserved pattern of crypt architecture and presence of thickened subepithelial collagen band. (Hematoxylin-eosin, 10x (A, B, D). C, detachment of the superficial epithelium and exposure of the subepithelial collagen band. (Hematoxylin-eosin, 10x).

### Histological findings

By definition, CC is characterized by thickening of the subepithelial collagen band to a thickness of more than 10 microns. (18) However, since measuring this band is time consuming and impractical, in addition to a description of increased thickness of the band, the key for diagnosis of CC is finding abnormal distribution of this band extending inside the lamina propria trapping capillaries and fibro-

blasts (Figure 4). (20) HE staining does not always make the distribution pattern of collagen obvious. In these cases, Masson trichrome staining is quite helpful. The presence of an abnormal collagen band by itself is not sufficient to diagnose CC. Other characteristics should be present. These include increased mononuclear infiltrate in the lamina propria (in some cases with abundant eosinophils), increased IEL levels (smaller increases than in LC) and damage to the superficial epithelium. In CC the superficial epithelium is

usually separated from the basal membrane which exposes the abnormal collagen band (Figure 5). (20)

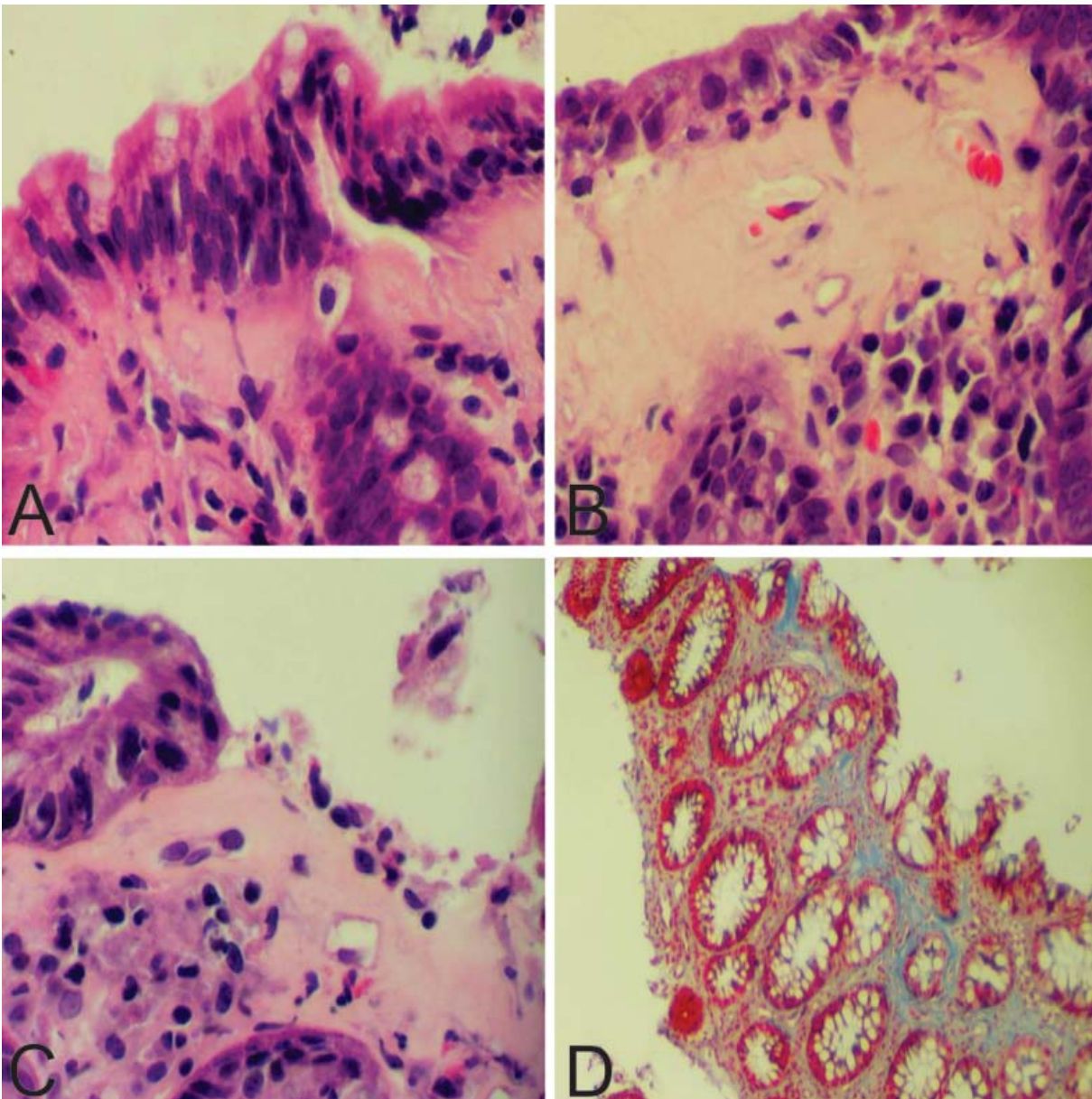
At this point it might be helpful to note that assessment of the subepithelial collagen band must be performed in a well-oriented biopsy because tangential cuts of the colonic mucosa may give the false impression of thickened mucosa.

As in LC, histological variants with no apparent prognostic significance have been described in cases of CC. These include pseudomembranous CC and CC with giant cells. Pseudomembranous CC is very rare. It is characterized by

fibrinopurulent pseudomembranes protruding from the mucosa in the context of typical CC. (29) CC with giant cells is typical CC with subepithelial CD68 + giant cells. (24)

### Differential Diagnosis

Other conditions that may appear with thickened subepithelial collagen bands include chronic ischemia, mucosal prolapse, diabetes mellitus and hyperplastic polyps. However, all of these lack accompanying inflammatory infiltrate. (30) CC



**Figure 5.** Histological features of collagenous colitis. A, mild superficial intraepithelial lymphocytosis. (Hematoxylin-eosin, x40). B, C, thickened subepithelial collagen band and denuded superficial epithelium (hematoxylin-eosin, 40x (B, C). D, trichrome positive staining for collagen fibers in the lamina propria of the abnormally thickened colon (blue). (Trichrome of Masson, 10x).



may appear with histological features similar to those found in IBD, such as distortion of the crypt architectural, cryptitis, Paneth cell metaplasia and isolated foci of superficial erosion of the mucosa. These appear on a mucosal base which is otherwise typical of CC. (25) Differentiating between CC and IBD is simple given that the crypt architecture is preserved in CC. However, CC and IBD are not mutually exclusive, and cases have been reported in which CC has progressed to ulcerative colitis while others have transitioned from ulcerative colitis to CC. (4, 5)

## CLINICAL COURSE OF LC AND CC

Between 20% and 48% of patients with LC have spontaneous clinical remissions, but have relapses after a 14 month follow-up. This suggests chronic and intermittent clinical development for at least for half of the patients. (31) CC has a very similar pattern with spontaneous clinical remissions in 25% of patients accompanied by improvements in histopathological findings. (31) Results of clinical remission of CC in 85.7% of patients treated through oral administration of budesonide have been described although relapses have been observed in up to 60% of them after oral treatment is stopped. (31) Thus, clinical course of CC is similar to that of the LC, chronic and intermittent.

## CONCLUSIONS

MC is a clinical and histopathological term that groups together LC and CC. It is used to describe a medical condition characterized by chronic watery diarrhea with colonic mucosa that appears to be normal when viewed endoscopically, but with histopathological findings consisting of increased mononuclear inflammatory infiltrate in the lamina propria, intraepithelial lymphocytosis, damage to the superficial epithelium which does not alter the architectural pattern of the crypts, and the presence of a thickened collagen band in the CC. Although the etiology is still uncertain, both LC and the CC have associations with autoimmune diseases and are more common in women. MCs incidence and prevalence have been increasing in developed countries, but there are still no exact figures for countries like Colombia. Nevertheless, pathologists must be able to recognize and diagnose these entities in order to provide suitable care for these patients.

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