Pitfalls and errors in the diagnosis of collagenous and lymphocytic colitis

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Abstract

The diagnosis of both CC and LC is based on a compatible clinical picture and well-established objective histological criteria. The motivation degree of the involved physicians is essential in the diagnosis of microscopic colitis. The gastroenterologist should refer every patient with chronic watery diarrhea to perform a colonoscopy in spite of the benign course of the disease and the absence of alarm symptoms or signs. The endoscopist should take multiple stepwise biopsy samples of the colonic mucosa despite that the mucosa looked macroscopically normal. Finally, the pathologist should be motivated to use objective histological criteria to make the diagnosis. In this context, it is important to define the terminology as clearly as possible to avoid confusion. © 2008 European Crohn’s and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

1. Introduction

Microscopic colitis is a term used to define those entities characterized by chronic watery diarrhea, normal radiological and endoscopic appearance, and microscopic abnormalities in the colon. The entity includes collagenous colitis (CC) and lymphocytic colitis (LC). CC differs from LC by a specific histopathological feature consisting of the presence of a subepithelial collagen band (10 µm or more) adjacent to the basal membrane. Both diseases display inflammatory changes in the lamina propria and superficial epithelial damage. They are considered chronic inflammatory diseases of the colon with a benign but sometimes relapsing course. Their low prevalence makes that they are registered in the list of rare diseases of the European Community (http://www.orpha.net).

2. Clinical and histological diagnostic criteria

The diagnosis of both CC and LC is based on a compatible clinical picture and well-established objective histological criteria. Clinical criteria include chronic or recurrent watery diarrhea of at least 1-month duration, and grossly normal or slightly abnormal (mild erythema and/or edema) full colonoscopy. The histological criteria are: (1) increased chronic inflammatory infiltrate (plasma cells, eosinophils and lymphocytes) in the lamina propria; (2) increased number of intraepithelial lymphocytes (IEL) (normal ≤ 7 per 100 epithelial cells); and (3) damage of surface epithelium, with flattening of epithelial cells and/or epithelial loss and detachment, and minimal crypt architecture distortion. Histological diagnosis of...
CC requires the additional presence of an abnormal surface subepithelial collagen layer with a thickness ≥ 10 µm, which entraps superficial capillaries and with an irregular lacy appearance of the lower edge of the basement membrane (Fig. 1A). A number of IEL higher than 20 lymphocytes per 100 epithelial cells in the absence of a thickened subepithelial collagen layer (<10 µm) is necessary to diagnose LC (Fig. 2). Immunohistochemistry for tenascin expression is used in doubtful cases, since it allows a better detection of the thickened subepithelial collagen layer (Fig. 1B).5

The frequency of the different clinical symptoms at diagnosis is described in Fig. 3. Chronic watery diarrhea is the hallmark in microscopic colitis. Urge to defecate and fecal incontinence are also very frequent. Associated symptoms include abdominal pain and flatulence, both of which are present in 60–70% of patients. The clinical presentation of microscopic colitis and diarrhea-predominant irritable bowel syndrome (IBS) might, therefore, be indistinguishable. Nocturnal diarrhea is also a symptom of microscopic colitis that rarely occurs in patients with IBS; however, it is only present in around 25% of patients with microscopic colitis.

There are no significant differences in clinical presentation between CC and LC.3 However, there are sex differences between both entities. In CC there is a clear female predominance, which is not as marked in LC (Table 1).4,6–9 Median age at diagnosis in the different population-based studies ranges from 58 to 68 years in CC, and 59 to 70 years in LC.4,6–9

There are other diseases which have been proposed to be included under the term of microscopic colitis. These atypical forms of microscopic colitis are listed in Table 2, and have been recently reviewed.10 Patients with clinical characteristics similar to those of classical microscopic colitis but with colonic biopsies disclosing chronic inflammation in the lamina propria and a mild increase in colonic IEL (without achieving the limits required for LC) are referred to as paucicellular lymphocytic colitis (also named microscopic colitis NOS).11 The other forms correspond to case reports and probably lack specificity to be considered as true entities.

3. Pitfalls and errors in the diagnosis of microscopic colitis

The motivation degree of the involved physicians is essential in the diagnosis of microscopic colitis. The gastroenterologist should refer every patient with chronic watery diarrhea to perform a colonoscopy in spite of the benign course of the disease and the absence of alarm symptoms or signs. The endoscopist should take multiple stepwise biopsy samples of the colonic mucosa despite that the mucosa looked macroscopically normal. Finally, the pathologist should be motivated to use objective histological criteria to make the diagnosis.

3.1. The gastroenterologist’s motivation

There is a generalised view that a patient with chronic watery diarrhea fulfilling the criteria of diarrhea-predominant IBS
achieved a 100% diagnostic yield. Another study assessed the distribution of the damage severity in the colon comparing the right and the left colon.\(^4\) The damage was similar in both colonic areas in 74% of CC patients and in 60% of LC patients. However, there was a predominance of right colonic damage in 22% CC and 27% LC, and of left colonic damage in 4% CC and 13% LC. Taking these two studies together one could recommend to take sample biopsies of at least three colonic segments — right colon (cecum plus ascending colon), transverse colon, and left colon (descendent plus sigmoid colon) — in separate sample tubes to obtain the maximum diagnostic yield.

The frequency of microscopic colitis in colonoscopies performed in patients with chronic watery diarrhea has been evaluated in different epidemiological population-based studies, ranging from 7.1% to 14% (Table 3). This figure is higher in the elderly, being more than 20% in patients aged 70 years or more.\(^7\)

### 3.3. The pathologist’s motivation

Microscopic colitis represents an area of difficult communication between gastroenterologists and histopathologists.\(^9\) The major problem is a vague definition or lack of definition.\(^20\) In this sense, the unhelpful term ‘non-specific colitis’ must be avoided since it is not clear what does it means. If the clinician receives a diagnosis of ‘non-specific colitis’, a non-specific treatment is prescribed. Conversely, if clinical data is lacking, the pathologist diagnosis will be ‘non-specific colitis’.

The subjective diagnosis of chronic inflammation in colonic biopsies may lead to normal biopsies from IBS patients being over-diagnosed as microscopic colitis. Thus, it is important to use objective criteria to define the terminology. The histological criteria for both CC and LC are well-established, and the clinician wants a specific diagnosis when takes multiple colonic biopsies to rule out microscopic colitis. The term ‘microscopic colitis’ has been proposed as an umbrella term for both conditions, CC and LC.\(^1\) Although therapeutic considerations for both variants of microscopic colitis are similar, we can only disclose the true incidence and epidemiological risk factors for both conditions with a specific diagnosis. On the other hand, there are several diseases with normal endoscopy and abnormal histology (intestinal spirochetosis, quiescent ulcerative colitis, infectious colitis, diverticular disease, non-steroidal anti-inflammatory drug-induced colitis). Although these conditions are covered by the definition, they are not considered as microscopic colitis. Therefore, the term microscopic colitis has scarce clinical value and should be avoided as a final

<table>
<thead>
<tr>
<th>Geographical area, years</th>
<th>CC</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Örebro, Sweden, 1984–93(^6)</td>
<td>9.0:1</td>
<td>–</td>
</tr>
<tr>
<td>Terrassa, Spain, 1993–97(^4)</td>
<td>4.8:1</td>
<td>2.7:1</td>
</tr>
<tr>
<td>Örebro, Sweden, 1993–98(^7)</td>
<td>7.5:1</td>
<td>2.1:1</td>
</tr>
<tr>
<td>Olmsted County, MN, 1994–01(^8)</td>
<td>6.7:1</td>
<td>1.6:1</td>
</tr>
<tr>
<td>Iceland, 1995–99(^9)</td>
<td>7.9:1</td>
<td>5.0:1</td>
</tr>
</tbody>
</table>

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**Figure 3** Frequency of the different clinical symptoms at diagnosis on a population-based cohort of microscopic colitis patients.\(^3\)

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**Table 1** Female: male ratio in collagenous and lymphocytic colitis in the epidemiological population-based studies

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**Table 2** Frequency of the different clinical symptoms at diagnosis on a population-based cohort of microscopic colitis patients.\(^3\)

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**Table 3** Frequency of the different clinical symptoms at diagnosis on a population-based cohort of microscopic colitis patients.\(^3\)

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**Table 4** Frequency of the different clinical symptoms at diagnosis on a population-based cohort of microscopic colitis patients.\(^3\)

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**Table 5** Frequency of the different clinical symptoms at diagnosis on a population-based cohort of microscopic colitis patients.\(^3\)
diagnosis in a pathological report. Several variants of CC and LC have been described but these are probably not specific entities. Rarely, chronic idiopathic IBD may have normal colonoscopic findings. This is known as minimal change colitis. Crypt architectural distortion is present and this condition behaves like ulcerative colitis.

It is important to be aware of the following caveats when making a diagnosis of CC or LC:

1. In health, the right colon has more lamina propria cellularity than the left colon. For this reason, biopsies from the right and left colon should be submitted in separate containers so that pathologists can avoid misinterpretation of this normal finding. If biopsies from different sites are put together for putative cost-effectiveness, minor degrees of CC and LC might be overlooked.

2. The thickened subepithelial collagen band in CC is patchy and increases in thickness towards the right side of the colon. In fact, rectal biopsies may be spared (i.e. normal) up to 40% of cases of microscopic colitis.

3. Subjective sensitivity in the estimation of collagen deposition is remarkably low, especially if applied to the threshold of 10 µm. Actual measurements performed on trichrome-stained slides allow an objective and accurate assessment.

4. A thickened collagen band is not sufficient to diagnose CC; the presence of trapped blood vessels and inflammatory cells within the collagen band, a ragged pattern of the inferior margin of the band, and intraepithelial lymphocytosis must also be present.

5. Improper biopsy specimen orientation can obscure CC, since clear-cut thickening of the collagen band is not demonstrable in oblique sections.

6. Metaplastic polyps usually have a thickened subepithelial collagen plate and diffuse chronic inflammation of the lamina propria.

7. Amyloid may present as a subepithelial eosinophilic band but the colonoscopy is often abnormal.

8. The indiscriminate use of the term ‘mild chronic inflammation’ should be avoided.

One of the pitfalls in the pathological diagnosis of LC is dealing with biopsies that show mild inflammation, but do not exhibit all features needed for a definitive diagnosis. This cases have been described as ‘paucicellular LC’ or ‘microscopic colitis NOS (not otherwise specified)’, being patchiness and a lower density of surface IEL the distinctive histological features. The hallmark of LC is increased IEL. The IEL count in normal colonic mucosa is about 5 IEL per 100 surface epithelial cells. In LC the IEL count increases to 20 or more per 100 surface epithelial cells. In some cases, however, IEL count in paucicellular LC may be higher than 20 IEL per 100 surface epithelial cells which may complicate the differential diagnosis from LC. In this situation, the patchy distribution of epithelial lymphocytosis, and the absence of flattening of epithelial cells, epithelial loss, and detachment may be useful to distinguish both conditions.

4. Conclusions

The diagnosis of both CC and LC requires a good relationship between the gastroenterologist, the endoscopist, and the pathologist. A better awareness of the disease by all the physicians involved and common diagnostic work-up protocols may help to increase the diagnostic yield of these diseases. In this context, it is important to define the terminology as clearly as possible to avoid confusion.

References


