Microscopic colitis

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Microscopic colitis

- The term is used as an umbrella term for two major conditions that are traditionally termed **lymphocytic colitis** and **collagenous colitis**

- Lymphocytic and collagenous colitis remain pathological diagnoses, but close correlation with both endoscopic and clinical data is essential for accurate assessment
Microscopic colitis: a history

1976 Lindstrom first described one common type: collagenous colitis

1980 Read recognised the association of normal endoscopy with inflamed biopsy material

1982 Kingham et al first coined the term microscopic colitis and suggested this term be used for this hitherto unrecognised group of conditions

1989 Lazenby et al first described the other common type: lymphocytic colitis

1993 Levison et al – review of 1982 cases and refined definition of term

2000s other subtypes described and recognised
Microscopic colitis as a concept

- normal colonoscopy
- chronic watery diarrhoea without blood
- significant, usually chronic, inflammation on biopsy
  - varied histological patterns
  - does it require colonoscopic normality?

- strong association with drugs
- diarrhoea is the commonest recorded complication of drug therapy
- how many cases are due to microscopic colitis?

- used to be considered rare
- now increasingly recognised throughout Europe and the World
  - I see 20-25 cases + a year
Microscopic colitis: Pathogenesis

- Still largely unknown

- Probably multifactorial: abnormal immune response + impaired intestinal barrier function (＞permeability) and myofibroblast dysfunction (in collagenous colitis)

- Smoking (smokers may develop their disease >10 years earlier than non-smokers)

- Drugs: > proton pump inhibitors and NSAID

- Autoimmune disorder: common association with autoimmune disorders including coeliac disease
Microscopic colitis: Epidemiology

- There is now considerable and increasing evidence (especially from Scandinavia) that these diseases (CC & LC) are common.

- As common as chronic inflammatory bowel disease in Sweden (each equal to CD with combined rate equal to UC).

- CC 4.9 per 10,000; LC 5.7 per 10,000.

- CC 75-90% female with mean age of 64.

- LC 60-70% female with mean age of 59.

Olesen et al, 2004
Microscopic colitis

- It is often misdiagnosed by pathologists as ‘mild chronic inflammatory bowel disease’, especially ulcerative colitis.

- True chronic inflammation infers a loss of the normal chronic inflammatory cell gradient in the lamina propria and basal plasma cells.

- The caecum shows an increased round cell infiltrate in the lamina propria and an enhanced intra-epithelial lymphocytosis, normally, and this should not be taken as evidence for microscopic colitis.
Collagenous colitis: pathology

- The collagen band should be in excess of 10 microns thick.
- Always wise to confirm with EVG stains and to rule out amyloidosis.
- The collagen band characteristically contains leucocytes and/or apoptotic debris (cf amyloidosis).
- CC more likely to be demonstrated in the right/transverse colon.
  
  *Offner et al 1999*

- A normal rectal biopsy does not rule CC out – in the appropriate clinical situation, always advise colonoscopy and right/transverse colonic biopsies (in 30% of cases the rectum is normal).
Collagenous colitis: pathology

- there is usually surface epithelial degeneration/stripping
- this may vary from subepithelial degeneration/vacuolation
- through extensive surface epithelial stripping
- to pseudo-membrane-like material on the surface
- ESPECIALLY in the right/transverse colon
Collagenous colitis

- there may be endoscopic abnormality

- mucosal tears
  
  Cruz-Correa et al, 2002

- submucosal dissection with gas evident on barium enema
  
  Mitchell et al, 2004

- modest pseudo-membrane material

- ESPECIALLY in the right/transverse colon
Collagenous colitis - associations

- rheumatoid arthritis
- scleroderma
- sicca syndrome
- thyroid disease
- no HLA association

- drug therapy: especially NSAIDs
- case control studies show strong relationship between long term non-steroidal anti-inflammatory agents (NSAIDs) and CC

*Riddell et al, 1992*

- other drugs: PPIs, H2 receptor blockers, carbamazepine, simvastatin, flutamide and ticlopidine
Collagenous colitis: treatment, natural history and prognosis

**Treatment**

- anti-diarrhoeals
- budesonide
- 5-ASA
- bismuth
- cholestyramine
- steroids
- 6-mercaptopurine, azathioprine
- surgery – faecal stream diversion

**Natural history & prognosis**

- highly variable from cure to long term debility
- budesonide excellent but often rapid relapse after cessation
- complete symptomatic remission in CC varies from 2% to 92%

*Bonner et al, 2000*
Lymphocytic colitis: clinical features

- chronic watery diarrhoea
- may be cramping abdominal pain
- general health usually good, without anaemia or raised serum inflammatory markers
- may suffer weight loss
- radiological and endoscopic examination normal
Lymphocytic colitis: clinical features

- occurs at all ages, including children, but typically in middle age
- commoner in women (M:F = 1:2.5)
- annual incidence
  - Orebro, Sweden, 2004  5.7/10,000
Lymphocytic colitis

- more evenly involves colon and rectum
- intra-epithelial lymphocytes > 20 lymphocytes per 100 epithelial cells
- T-lymphocytes: CD3 + CD8 +
- lamina propria chronic inflammation
- acute inflammation may be present
- can miss it at lower power
Lymphocytic colitis

- more than 20 per 100 epithelial cells
- Increase of cellularity in the lamina propria (with loss of the normally decreasing inflammatory cell density towards the muscularis mucosae)
Intra-epithelial lymphocytes
(surface, median per 100 epithelial cells)

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<tr>
<td>lymphocytic colitis</td>
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</table>
Key histological features of microscopic colitis

Lymphocytic colitis

• An increased number of surface intraepithelial lymphocytes ( > 20 per 100 epithelial cells)
• Mild surface epithelial injury (vacuolization, flattening and mucin depletion)
• Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
• Focal inflammatory bowel-disease –like changes (cryptitis and Paneth cell metaplasia) possible
• No or little crypt architectural distortion
• Thickening ( <10 µm) of the subepithelial collagen band may be present

Technical note: HE stained slides are generally sufficient to make the diagnosis; CD3 immunostaining may highlight intraepithelial lymphocytes, but is not needed routinely. Only IELs in the intercryptal spaces should be considered. The epithelium overlying lymphoid follicles should not be evaluated
Key histological features of microscopic colitis

Collagenous colitis

• Thickening (>10 µm) of the subepithelial collagen band (> in the right colon; rectosigmoid may be normal)
• Marked surface epithelial injury (flattening and detachment)
• Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
• Focal inflammatory bowel-disease–like changes (cryptitis and Paneth cell metaplasia) possible
• No or little crypt architectural distortion
• An increased number of surface intraepithelial lymphocytes (< 20 / 100 epithelial cells) may be present

Technical note: HE stained slides are generally sufficient to make the diagnosis; collagen stains or tenascin immunostaining may highlight the thickened collagen band, but are not needed routinely.
Incomplete and variant forms

Patients who have clear clinical features of microscopic colitis but fall short of fulfilling the morphological criteria for LC or CC (incomplete forms of microscopic colitis)

**Incomplete lymphocytic colitis** (syn. Paucicellular or borderline lymphocytic colitis) with an increased number of IEL (<20 / 100 EC) and increased mononuclear inflammation in the lamina propria

**Incomplete collagenous colitis** (syn. minimal collagenous colitis) with thickening (<10μm) of the subepithelial collagen band and increased mononuclear inflammation in the lamina propria

**Variant forms of microscopic colitis:**
- Cryptal lymphocytic colitis
- Lymphocytic colitis with giant cells
- Collagenous colitis with giant cells
- Pseudomembranous collagenous colitis
Lymphocytic colitis - associated features

- sero-negative, non-destructive arthritis
- auto-immune disease
- drugs
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - ranitidine, lansoprazole (anti-acid)
  - ticlopidine (inhibitor of platelet aggregation)
  - flutamide (anti-androgen)
  - rutoside, cyclo-3-Fort (phlebotonic)
Lymphocytic colitis - treatment

- loperamide
- cholestyramine
- sulphasalazine
- 5-ASA
- metronidazole
- corticosteroids
- budesonide
- gluten-free diet
Lymphocytic colitis – natural history

- chronic intermittent 30%
- chronic continuous 7%
- single attack 63%
- rectal sparing 30%
- family history of IBD 12%
Lymphocytic colitis – differential diagnosis

- normality – easy to overcall – clinical and endoscopic context critical
- do not call it ‘mild’ chronic inflammatory bowel disease
- one very rare but important differential diagnosis
Lymphocytic colitis – differential diagnosis
Lymphocytic colitis – differential diagnosis

- epitheliotropic T-cell lymphoma
- rare in small intestine, even rarer in large intestine
Differential diagnosis and relationship with chronic inflammatory bowel disease

- Collagenous colitis: ischemia, radiation-induced injury and amyloidosis:
- Infectious disease
- Post-dysenteric irritable bowel syndrome
- Drug-induced changes (>NSAR)
- IBD: absence of significant crypt distortion; colonoscopic abnormalities clinical and endoscopic correlation are critical: bloody diarrhoea will not be microscopic colitis!
Lymphocytic colitis and collagenous colitis

◆ similar:
  - age
  - autoimmune diseases
  - arthritis
  - diarrhoea & abdominal pain
  - NSAIDs and aspirin

◆ dissimilar:
  - sex ratio (CC more females)
  - smoking (LC patients more often non-smokers or ex-smokers)

Baert et al, 1999
Lymphocytic colitis – associations

- coeliac disease: 20-40% either way
- lymphocytic gastritis
- less strong association with auto-immune disease (unlike CC)
- no HLA association
- drugs, especially NSAIDs
- others: PPIs, antibiotics, etc
Collagenous colitis and lymphocytic colitis – associations

- cases are described of LC becoming CC
- most cases stay pure
- both associated with certain causes – especially drugs
- similar treatments successful (in some patients)
- other associations not similar (LC and coeliac disease)
That's all Folks!
A touch of reality?

“my approach to all GI biopsies is to ignore small inflammatory things, since they are not specific diseases and they mean nothing to clinicians, unless the report is accompanied by a long, long comment explaining what these tiny insignificant things mean.”

Henry D Appelman