What is colitis?

Pitfalls in the microscopic diagnosis

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What is colitis?

Statistical approach (morphometry)?

• Chronic inflammatory infiltration
total cellularity increase

• Surface epithelial height to crypt epithelial height.
In normal mucosa the surface epithelial cell height exceeds the height of crypt epithelium

• Redistribution of infiltrating cells so that there is a similar density in the basal third to that of the superficial third > IBD

Jenkins e.a. J Clin Pathol 1988; 41; 72-79
Normal mucosa vs Colitis

- Lamina propria cellular infiltrate: increase in intensity; composition & distribution
- Organized lymphoid tissue: increase, stimulation
- Epithelial cells:
  - surface epithelium: terminally differentiated cells
    DAMAGE & REPAIR (restoration)
  - crypts: differentiating cells, proliferative compartment
    INCREASED PROLIFERATION (mitotic activity)
  - normal turnover: increased turnover

Basic lesions: Inflammation

- **Inflammation pattern I**
  - Patchy, focal
  - Diffuse
Basic lesions: Inflammation

- **Inflammation pattern II**
  - Diffuse upper third (Infections such as Shigella colitis)
  - Diffuse transmucosal (IBD)

Basic lesions: Architecture

- Surface
  - Flat or irregular
Basic lesions: Architecture

- Crypt architecture
  - Crypt density
    - 7/8 crypts per 1 mm mucosal length (IBD 4 to 5)
    - Closely packed
  - Variable or constant intercryptal distance

- Crypt architecture
  - Straight or branching tubes (infrequent branching < 10% may be normal)
  - Base reaching muscularis mucosae
  - Variable or constant internal diameter
- Muscularis mucosae
Clinical Situations
Immunocompetent - Immunocompromized

- No clinical information
  - Non specific colitis
- Chronic diarrhea and normal endoscopy
- Inflammatory diarrhoea
  - Infectious colitis
  - Drug-induced colitis
  - Inflammatory bowel disease
  - Miscellaneous

No clinical information

“Non-specific inflammation”
Tanaka & Riddell, Hepato-gastroenterol 1990; 37: 18-31
- Predominantly chronic inflammatory cell infiltrate in the absence of architectural distortion and multiple basal lymphoid aggregates or plasma cells immediately above the muscularis mucosae.
- Such a pattern can be seen in resolving infections, complicated diverticular disease, drug-induced colitis and bile-salt malabsorption, but may include CD. However, it is currently impossible to make a positive diagnosis of CD in these circumstances, although in a patient with known CD the lesions may well represent local involvement.
No clinical information

“Non-specific inflammation”
- Increase in inflammatory cells beyond what would be expected physiologically in the corresponding anatomic sites. Crypts may show reactive changes, such as an increase in mitoses and slight irregularity in shape.
- Lack of sufficient clinical data or distinctive histopathological features precludes further classification into specific etiologic types of colitis.

No clinical information

“Non-specific inflammation”
- No significance
- No clinical implications as far as treatment is concerned
- Do not use it

- Lou e.a. Hum Path 1971; 2; 421
  Colonic histiocytosis:
  34/50 (68%) consecutive rectal biopsies: small collections of PAS+ cells
- Bejarano e.a. Am J Surg Pathol 2000; 24; 1009
  40% of biopsies +; associated changes point to healing phase
Normal endoscopy and chronic diarrhea
The spectrum of “microscopic colitis”

Infections
Post infectious IBS
Drug-related disease

Allergy-associated colitis
IBD
Minimal change colitis
IBD in remission

Microscopic colitis (?)
- Collagenous colitis
- Lymphocytic colitis
- Variants
  - Giant cell colitis
  - Pauci-IEL lymphocytic colitis
  - Apoptotic colopathy
  - Mastocytic (entero)colitis
  - Pseudomembranous variant

Human Intestinal Spirochetosis

- >
- Less common in children ?
- Usually asymptomatic
- Pathogen/commensal ?
- incidence in homosexual men and immunocompromised (AIDS) pts
Infections & Colitis

- Enterohemorrhagic E. coli: important in western world
- Lesions in terminal ileum and colon
- Microscopy

<table>
<thead>
<tr>
<th>Normal</th>
<th>Acute inflam</th>
<th>Ischemic type</th>
</tr>
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<tbody>
<tr>
<td>12 / 31</td>
<td>10 / 31</td>
<td>5 / 11</td>
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Combination: Pseudomembranous colitis
4 / 11


Post infectious IBS
25% of pts with Campylobacter colitis

CD3 staining lamina propria lymphocytes.

***p<0.001 v controls. Spiller e.a. Gut 2000; 47; 804
Drug-Induced Colitis: The Problem

- Diarrhoea is a frequent adverse event of drugs
  - 7% of all drug adverse effects
  - 4.1% in 5,669 pts with lansoprazole
- More than 700 drugs have been implicated in causing diarrhoea
- Clinical presentation
  - Acute Diarrhoea: Usually during the first days of treatment
  - Chronic Diarrhoea: Can appear long time after start of drug
- Colitis is less common and associated with less drugs

Drug-Induced Colitis
Different Patterns

- Normal biopsy - oedema
- Eosinophilic colitis
  - Aspirin; Psychotropic drugs (carbamazepine); Ticlodipine
- Microscopic colitis (Lymphocytic more common)
  - Proton pump inhibitors H2 receptor antagonists
  - NSAIDs Ticlodipine
  - Veinotonics
- Others
**Microscopic colitis**

- **Collagenous colitis**
  - Discontinuous thickening of subepithelial collagen table
  - Increase in lamina propria cells
  - Changes with treatment
- **Lymphocytic colitis**
  - Normal architecture
  - Flattened – cuboidal surface epithelial cells
  - Increase in interepithelial lymphocytes (>20/100)
  - Increase in lamina propria cells

Biopsies of the whole colon are required as sigmoid and rectum may fail to show significant thickening of collagen band
- Jessurun e.a. Hum Pathol 1987; 18; 839
- Offner e.a. Hum Pathol 1999; 30; 451

Staining for tenascin may be useful for the diagnosis of minimal collagenous colitis
- Muller e.a. Virch Arch 2001; 438; 435-41
Collagenous & lymphocytic colitis

• Heterogeneous disease etiologically
  – Idiopathic
  – Infections (campylobacter?)
  – Drugs
  – Gluten
  – Autoimmune disease

Microscopic (collagenous and lymphocytic) colitis & IBD

– 26 pts with a diagnosis of IBD and microscopic colitis (based on a review of 12 centres: 9 Europe; 3 North America)
  • Panaccione e.a. Gastroenterology 1999; 116: A833
  • Geboes IOIBD, unpublished
– Progression towards Ulcerative colitis
  • 4 pts: elderly patients, pancolitis, Geboes IOIBD
  • Pokorny e.a. J Clin Gastroenterol 2001; 32; 435
– Progression towards Crohn’s disease
  • 2 pts: Geboes IOIBD
– Healing (?) after IBD
Inflammatory diarrhea

Acute unclassified colitis (6 wks duration) Notteghem e.a.
Gastroenterol Clin Biol 1993, 17, 811-815
104 pts; follow-up : 2.5-3yrs
results :
– 16 Lost for follow-up
– 88 - 46 (52.3%) > IBD
  54% = UC  33% = CD
  13% = Unclass
- 42 (47.7%) > no relapse

Infected-type colitis
Spectrum of microscopic features

– normal biopsy
  toxins
  • Vibrio ch; Klebsiella
– oedema
– active inflammation
  invasion
  • Yersinia, Campylo
– fulminant lesions
  (extensive necrosis)
– residual lesions
Infective-type colitis
Microscopic features

• Architecture
  – NORMAL (except ...) String of Pearls

• Inflammation
  – DISTRIBUTION: focal – patchy
  – COMPOSITION
    • NEUTROPHILS (active acute)
      – early (day 1-7) Superficial upper part of lamina propria & upper part of crypts
    • MONONUCLEAR CELLS
      – late (day 9, 10)
      – superficial (except...)

IBD and infection at diagnosis

First attack of colitis

• ASLC group 78% + culture
• IBD group 21% + culture

Schumacher e.a. Scand J Gastroenterol 1993, 28, 1077-85
Colonoscopy in inflammatory diarrhea
Where to biopsy? How many?

**Number of samples** (Bentley e.a. J Clin Pathol 2002, 55; 955)

**Material & Methods**
- 25 pathologists
- 60 cases with follow up (rectal & full colonoscopic series)

**Results**

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<thead>
<tr>
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<th>Rectum</th>
<th>full series</th>
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<tr>
<td>Crohn’s disease</td>
<td>24%</td>
<td>&gt; 64%</td>
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<tr>
<td>Ulcerative colitis</td>
<td>64%</td>
<td>&gt; 74%</td>
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**D.D Chronic Idiopathic Inflammatory Bowel Disease - Acute Self Limiting (Infectious type) Colitis**

- Surawicz e.a. 1984 : 148 pts, (44) - (22 short course IBD, 82 long course, 26 CD)
  - 75% of CD : crypt distortion
- Nostrant e.a. 1987 : 168 pts, (48) - (36 short course - 84 long course UC)
  - Histopathology differentiates ASLC from UC (crypt distortion - plasmacytosis)
- Therskilden e.a. 1989 : 32 pts
  - lesions absent at 1 mth, no predictive value
D.D Chronic Idiopathic Inflammatory Bowel Disease - Acute Self Limiting (Infectious type) Colitis

Basic lesions

mucosal architecture
  • regular - irregular surface
  • crypt distortion

inflammatory infiltrate
  • basal plasmacytosis

Chronic Idiopathic Inflammatory Bowel Disease
Ulcerative colitis
Biopsy Diagnosis & IBD - Evolution in Time
Schumacher e.a. Scand J Gastroenterol 1994

Colonoscopy in inflammatory diarrhea
Repeat Endoscopy!

• Repeat endoscopy can help to establish a precise diagnosis
  – 12 pediatric pts with indeterminate colitis > UC Markowitz Am J Gastroenterol 88; 1993
  – 14% (out of 96) developed a pattern more consistent with UC Langevin e.a. Am J Gastroenterol 15; 1992

• Repeat biopsy can help to establish a precise diagnosis
Mimics of Crohn’s disease/IBD

- Crohn’s disease is a discontinuous disease
- Various subtypes of (ileo-)colitis have also a segmentary distribution
- Most of conditions that mimic Crohn’s disease are rare (often isolated case reports)
- Infections
  - Acute diarrhoea
  - Chronic
- Drug-induced colitis
- In children
  - Glycogen storage disease type Iib
  - Possibly chronic granulomatous disease
- Solitary rectal ulcer syndrome
- Ulcerative colitis
  - Crohn’s disease with UC-like phenotype
  - Resolving UC
- Miscellaneous
  - Diverticular disease-associated colitis
  - Vasculitis
  - Endometriosis
  - Enterocolitis in seronegative spondylarthropathies

Yersinia enterocolitis
Intestinal Tuberculosis
Drug-induced colitis and IBD

• Granulomatous disease
  – Diclofenac
  – Clofazimine
  – (Baert e.a. 1995) (Karat 1975)

• Non-granulomatous disease
  – Immunosuppressives
  – NSAIDs
  – Chemotherapeutic agents
  – Miscellaneous

Drug-Induced Colitis: Patterns

• IBD-like pattern: Crohn’s disease without granulomas
  – Mycophenolate mofetil

• IBD-like pattern: Ulcerative colitis
  – Diclofenac
  – Amionoglutethemide (antineoplastic agent)
Mofetil Mycophenolate & Chronic diarrhoea

• 3/20 pts with Crohn’s disease
  Hafraoui e.a. Gastroentérol Clin Biol 2002, 26, 17
• 26 pts (mean age 41.5yrs) with cadaveric organ transplant > persistent afebrile chronic diarrhoea
  – 13 infections (Campylobacter, CMV ..)
  – 13 Crohn’s-like morphology
**Diverticular disease-associated Colitis**

- Chronic colitis localized to the sigmoid colon and occurring in association with diverticular disease (Makapugay & Dean Am J Surg Pathol 1996, 20, 94-102; Ludeman & Shepherd Pathology 2002; 34; 568-572)
- Pathogenesis: multifactorial (mucosal prolapse, ischemia..)
- Microscopy
  - crypt distorsion, basal plasmacytosis > UC-like
  - fat wrapping, fissures - sinuses, granulomas > CD-like
    (Goldstein e.a. Am J Surg Pathol 2000, 24, 668-675)
  - no lesions proximal and distal
- Outcome
  - 3 / 23 > UC (Makapugay)
  - 2 / 25 > CD (Golstein)

**Vasculitis**
Endometriosis (CK7)

- Mucosal changes with endometriosis > misdiagnosis of colitis
  - Ulceration, gland distortion, crypt abscess, increased inflammatory cell infiltrate, irregular smooth muscle fibers: 8/10
  - Focal distribution
  - Related to endometrial deposits: 7

Langlois e.a. Hum Pathol 1994; 25: 1030-4

Inflammation & Spondylarthropathy

- Histopathology of intestinal inflammation related to reactive arthritis Cuvelier e.a. Gut 1987
  65% reactive arthritis; 57% ankylosing spondylitis (n = 232)

  Evolution towards CD: 7% (n = 49)
UC & CD

• Crohn’s disease and UC-like phenotype
• Cryptolytic granulomas in Ulcerative colitis?
• Long-term evolution of UC

Indeterminate colitis or IBD unclassifiable?

Indeterminate colitis - Definitions used in Pathology

• - Colectomy specimens showing overlapping features of Crohn’s disease and ulcerative colitis or data are insufficient to make a decision.(Kent e.a. 1970)
• - Colectomy specimens showing overlapping features of both Crohn’s disease and ulcerative colitis.(Price et al 1978)
• - Colectomy specimens in whom a clear pathologic distinction between ulcerative colitis and Crohn’s disease is impossible (because of failure to recognize or accept certain criteria as indicative of Crohn’s disease or because of the absence of adequate clinical and radiographic material or because of inadequate biopsy material).(Odze et al 2004)
• - Inability to make a confident diagnosis of the pattern of colitis despite examination of an adequate surgical resected or adequate mucosal biopsy series from the colon and rectum.(Price et al 1996)
Indeterminate colitis

Definitions used in Pediatrics

- A history of chronic colitis compatible with both the diagnosis of CD or UC. (Auvin et al 2005)
- Colitis that cannot definitively be declared as CD or UC based on clinical history, physical examination, endoscopic appearance, histologic findings and radiologic studies. (Heyman et al 2005)
- Endoscopy and histopathology are either inconclusive or divergent with regard to the diagnosis of UC or CD. (Bentsen et al 2002)
- Exclusive inflammation of the large bowel and neither endoscopic nor histologic findings typical for CD or UC. (Pozler et al 2006)

Definitions used by Gastroenterologists – Surgeons - Epidemiologists

- A disease with “clear” evidence of inflammatory bowel disease but insufficient evidence to make a definite diagnosis of either UC or CD. (Ekbom 2000)
- Diagnosis based on a double-contrast barium enema examination, endoscopy, and histopathology being conclusive for a diagnosis of IBD but inconclusive for a diagnosis of either definite UC or CD. (Matsui et al 2003)
- Patients who have the clinical and macroscopic features of either CD or UC, both pre- and per-operatively. The histology remains indeterminate both pre- and post(per)operatively (includes mucosal biopsies and colectomy specimens). (Kangas et al 1994)
**Indeterminate colitis**

Definitions used by Gastroenterologists – Surgeons - Epidemiologists

- Patients with mucosal ulcerative colitis with histologic features of CD such as skip lesions, transmural inflammation, granulomata or mucin depletion but no clinical or radiological evidence of CD. (Pishori et al 2004)

- Colitis, for which endoscopic, histologic and radiologic criteria fail to discriminate between UC and CD of the colon. (Burakoff 2004)

- Colitis for which there is no identifiable cause and with clinical features of both UC and CD.

**WCOG and IOIBD Proposal for classification**

- When the diagnosis is based upon evidence including colectomy specimens
  - Colitis of known type or etiology (UC, CD, ...)
  - Colitis with (some) features of CD (see text)*
  - Colitis of uncertain type etiology – no features of CD (If “Indeterminate colitis” is used at all this is the group it should be applied to)
- Colitis not classifiable with the available material
- When the diagnosis is based upon evidence including mucosal biopsy samples
  - Colitis of known type /etiology (UC, CD etc)
  - Colitis type unclassified (IBDU)
  - Colitis of uncertain etiology (Possible IBD)
  - Colitis non classifiable with the available material
- * Implications for potential IPAA
CD or CD
B-1451209

- Male pt 50 yrs
  - 1984: colitis, not classified
  - 1988: weight loss, diarrhea
  - Small intestinal biopsy: complete villous atrophy & epithelial lymphocytosis; serology = negative
- Diagnosis: Coeliac disease
- 1989: patchy colitis, not classified; ileum = normal
- 2005: colonoscopy: ileum: normal; colon mild hyperemia; biopsies: near normal
- 2007: Hospitalization for subobstruction: ulcerative jejunitis
- Family History of Crohn
- Surgery: Diagnosis on operative specimen Crohn’s disease

IBD & Therapy

- Improvement
  - Decrease of score
  - Disappearance of activity defined by the presence of neutrophils?
- Remission
  - Healing
  - Disappearance of inflammation – persistent architectural abnormalities?
  - Normalisation has been observed in UC (and CD?)
Crohn’s disease before and after remicade