The Importance of clinicopathological confrontation in Inflammatory bowel disease

K. Geboes, MD, PhD, AGAF
Diagnostic issues
- Initial onset
- Young children
- Concomitant liver disease
- Mimics of IBD
  - Endometriosis
  - Diverticular disease associated colitis
- ...

Complications
- Clostridium difficile
- CMV

Diagnosis & Treatment
- Crohn versus UC

Difficult issues
- Isolated ileitis – small intestinal involvement and diagnosis of Crohn’s disease
- Upper GI involvement – focally enhanced gastritis – and differential diagnosis of Crohn’s disease and ulcerative colitis in young children
- Fulminant disease
Basic clinical information required

**Major**
- Age of patient
- Origin – location of biopsy samples
- Male or female
- Duration of symptoms – history
- Any form of treatment

**Minor**
- Sometimes: results of lab analysis (features of malabsorption...)
- Type of symptoms (watery or inflammatory diarrhea)
AGE &

Symptoms: Watery or inflammatory diarrhea
Female patient °1944

Clinical History
- Stenosis of a renal artery and the celiac trunk
- Arterial hypertension
- Migraine

Treatment: Cafergot, omeprazole, tiberal, plavix (clodipogrel)

Current complaints: headache and watery diarrhea

Endoscopy: Ischemia? > normal aspect
FEMALE PATIENT 1944

Ileal biopsy: flattened villi, ileitis(?)

Diagnosis

Age: Crohn’s disease less likely
Watery diarrhea: Crohn’s disease less likely
Drugs: Crohn’s disease less likely

MICROSCOPIC ILEOCOLITIS
Age & Initial onset
Duration of symptoms

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
INITIAL ONSET

Clinically only age (younger age) suggestive of IBD
Initial diagnosis
Diagnostic problems

Early onset
Adults
Lesions take 4 to six weeks to develop

Young children
- Basal plasmacytosis: 58%
- Lesions are discontinuous in UC
- Architectural abnormalities often absent

Ulcerative colitis in children

- Colonic biopsies from children with new onset UC show significantly less abnormalities

- Focal active colitis and/or absence of crypt abnormalities is observed in 33% of patients in the initial biopsies

- Rectal sparing is more common

- In 4-8% of cases the initial biopsy is normal
Colitis unclassified (IBDU)
Indeterminate colitis (IC)

- 509 cases of childhood IBD
  - 367 : CD
  - 122 : UC
  - 20 : Indeterminate (4%)
- 202 cases
  - 45 : IC (9.8%)

The percentage of cases diagnosed as IC in children varies between 4 and 23%
IC is more prevalent in the very young (up to 33% in patients younger than 2 yrs)
Reclassified cases are more commonly UC

UC & Liver disease
Concomitant liver disease

- Rectal sparing and patchy colitis or focal inflammation are more common in patients with PSC without clinically overt colitis
  - Loftus e.a. Gut, 2005; 54; 91
- PSC affects 2-7% of UC patients
- 75%-100% of patients with PSC have UC
- The frequency of hepatitis in IBD pts varies from 1-16%

- This is also observed in other types of chronic liver disease
  - D. Awad, Thesis, Lille
Mimics

In evolutionary biology, mimicry is the similarity of one species to another which protects one or both. This similarity can be in appearance, behaviour, and even location,

Age and location of biopsy samples

A planthopper mimics a leaf
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
- no lesions proximal and distal
Outcome
- 3 / 23 > UC (Makapugay)
- 2 / 25 > CD (Goldstein)
Mimics

Male or female

Drugs?
Endometriosis

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
Crohn’s disease and endometriosis
Craninx e.a. Eur J Gastroenterol Hepatol 2000; 12: 217

- In Crohn’s disease endometriosis of the terminal ileum seems more common
- Endometriosis can mimic Crohn’s disease
- Endometriosis can occur simultaneously

- 8 female pts: surgery for Crohn’s disease of terminal ileum (n=7) or colon (n=1)
- Intestinal endometriosis of the ileum (n=6); colon (n=2)
Drug-Induced Colitis: PATTERNS

• IBD-like pattern: Crohn’s disease without granulomas
  - Mycophenolate mofetil
  - Isotretinoin (and analogues) for treatment of acne
  - Induce colitis (which regresses after stopping but reappears upon challenge)
  - Colitis may appear after stopping (IBD type: UC/CD/IBDU)
  - Relationship with IBD(?) Shale et al Gut 2009 p 737

• IBD-like pattern: Crohn’s disease with granulomas
  - Diclofenac
  - Clofazimine

• IBD-like pattern: Ulcerative colitis
  - Diclofenac
  - Amionogluthemide (antineoplastic agent)
Isotretinoin and intestinal inflammation

Pharmacovigilance – FDA Medwatch
1997-2002: 85 cases of IBD (36 UC; 30 CD; 19 Unclassified)
2004-2008: 369 cases (155 UC; 106 CD; 108 IBDU)

Mechanisms
Isotretinoin has an effect on vit A levels
Retinoids inhibit neutrophil and monocyte chemotaxis, and production of oxygen species (innate immunity)
Retinoids also affect acquired immune response
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Complications

- Clostridium difficile
- CMV
Complications

SD, male 40 yrs. old. (680718M467.)

-2002: Rectal blood loss, UC? (no definite diagnosis) rectal mesalazine

-June 2008: Recurrence of rectal blood loss and urgency

Total colonoscopy: ulcerative rectitis, Mayo 2, otherwise normal
Biopsies suggestive of ulcerative colitis
Treated with oral mesalazine, no response
Rectal mesalazine added (4 g enema)

-Oct 2008: Hospital admission
Abdominal pain, diarrhea (10x/d, 2x/night), fever (38°C), rectal blood loss

Sigmoidoscopy: active rectitis, up from 10 cm normal vascular pattern, islands of mucopus, pseudomembranes

Stool enteropathogens on day of admission
-C diff toxine A/B negative, parasites negative
-other pathogens: no reply yet
SD, male 40 yrs. old.

Levofloxacine 500 mg bid and Metronidazole 500 mg tid started
IV fluids/electrolytes, bowel rest

Day 3: no improvement, CRP 144 mg/L (60 mg/L on admission)

Second stool sample (repeated on day 1): *C diff* toxine A/B positive

CT abdomen: Pancolitis with max. luminal diameter of 6 cm.
Complications


- Retrospective single referral center cohort on the incidence of CDAD in IBD and non-IBD patients

- Recruitment period
  - January 2000 → December 2007
  - Two periods of equal duration
    - 01/2000 - 12/2003
IBD and C difficile colitis

- IBD patients significantly younger (p = 0.001)
- IBD patients acquired infection more in outpatient setting (p = 0.14)
- IBD patients took
  - less AB in the prior 3 months (p = 0.047)
  - more immunomodulators (p < 0.001)
  - Acid suppression no difference
- IBD patients had less co-morbidity (p = ns)
- No pseudomembranes were seen in IBD patients
- Hospital stay in IBD was shorter (p < 0.001)

Absence of pseudomembranes in Clostridium difficile-associated diarrhea in patients using immunosuppression agents.
- Nomura K e.a. Scan J Gastroenterol 2009; 44: 74-8
Content

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<table>
<thead>
<tr>
<th>CROHN’S DISEASE</th>
<th>ULCERATIVE COLITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal/discontinous chronic (lymphocytes and plasma cells) inflammation</td>
<td>basal plasmacytosis (defined as presence of plasma cells around (deep 1/5th of lamina propria) or below the crypts (subcryptal))</td>
</tr>
<tr>
<td>Patchy chronic inflammation</td>
<td></td>
</tr>
<tr>
<td>Focal crypt irregularity</td>
<td>heavy, diffuse transmucosal lamina propria cell increase</td>
</tr>
<tr>
<td>Granulomas (not related to crypt injury) are generally accepted diagnostic microscopic features</td>
<td>widespread mucosal or crypt architectural distortion.</td>
</tr>
</tbody>
</table>
Patchy inflammation
CD

Diffuse inflammation
UC
Treatment has an impact upon the distribution of inflammation

UC prospective studies

- 13/39 histologic evidence of patchiness
  (5 - 13% : rectal sparing)
- 7/13 patchiness following steroids
- patchy and nonpatchy group : no difference in rectal therapy
  - Bernstein e.a. Gastrointest Endosc 1995
- heterogeneous distribution after budesonide : 11%
- loss of proximal to distal gradient
**TREATMENT AND IBD**

Loss of diagnostic features

- Distribution of inflammation becomes discontinuous
- This can also occur due to the natural history of alterations of remission and relapses

Therefore it is essential to know

- The duration of symptoms (days, weeks or years)
- Previous treatment
Isolated small bowel involvement

Wireless Capsule Endoscopy

Normal jejunum
### Isolated small bowel involvement

**Ileocolonoscopy & Isolated ileitis**

<table>
<thead>
<tr>
<th>Small bowel lesions are common</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å Elderly patients with a history of joint lesions</td>
<td>Å NSAIDs ulc</td>
</tr>
<tr>
<td>Å Abdominal surgical history</td>
<td>Å Adhesion</td>
</tr>
<tr>
<td>Å General symptoms/ systemic disease</td>
<td>Å Vascular diseases</td>
</tr>
<tr>
<td>Å General symptoms</td>
<td>Å Infections</td>
</tr>
<tr>
<td>Å No features</td>
<td>Å Tumors:</td>
</tr>
<tr>
<td>ï Age of the patient</td>
<td>ï neuroendocrine tumor of ileum</td>
</tr>
<tr>
<td>ï No malabsorption in clinical chemistry</td>
<td>ï Metastasis</td>
</tr>
<tr>
<td>ï Short history</td>
<td></td>
</tr>
</tbody>
</table>
Upper GI involvement and UC or CD

- Porto criteria for the diagnosis of Pediatric IBD
- Indeterminate colitis can only be diagnosed after a full diagnostic work-up. This must include colonoscopy with intubation of the terminal ileum, upper gastrointestinal endoscopy and small bowel follow through. J Ped Gastroenterol Nutr 2005; 41: 1-7

- Focally Enhanced gastritis
  - Clinical Significance
    - Children
      - Genuine positive predictive value
    - Adults
      - 34 cases out of 971 series of gastric biopsies (3.5%)
      - 4/34 (11.8%) have IBD
      - 2/4 have Crohn’s disease
      - Positive predictive value 5.9%
        - Xin & Greenson Am J Surg Pathol 2004 adults
Focally Enhanced gastritis
Apthoid gastritis
Gastritis and Ulcerative colitis

54 children with IBD (Castellaneta et al 2004)

- 34/54 (63%) : Crohn’s disease
- 18/54 (33.3%) : Ulcerative colitis
- Upper GI inflammation
  29/54
    - 22 Crohn
    - 7 (38.9%) Ulcer colitis
Gastritis and Ulcerative colitis

Diffuse gastritis is a common finding in pediatric patients
- Hendrickson 2003 (statement)
- Ruuska 1994
- Tobin 2001
- Berrebi 2003
- Castellanata 2004

Focally enhanced gastritis is reported in up to 20% of pediatric patients with ulcerative colitis
- Sharif et al 2002
- Kundhal et al 2003
Upper GI involvement and UC or CD

- Upper GI lesions in ulcerative colitis are different in children and adults
- Gastritis is common in children with ulcerative colitis
- The diagnostic value of gastritis in ulcerative colitis has not yet been established; the predictive value is low in adults
- Two patterns have been recognized
  - Diffuse gastritis
  - Focally enhanced gastritis
Severe upper small intestinal inflammation can complicate severe ulcerative colitis
Fulminant colitis

- Stools per day >10
- Continuous blood
- Temperature >37.5
- Pulse > 90
- Hemoglobin: transfusion required
- Dilated colon
- Abdominal tenderness
Fulminant colitis

- Ulcerative colitis
  - First attack
  - Exacerbation

- Crohn’s disease

- Other types
  - Infection
  - Pseudomembranous colitis
  - Ischemic colitis
  - ....

- Treatment
  - Colectomy with IPAA or not

- Role of pathologist
  - Look for CMV
  - Diagnosis
    - UC, CD or other
Conclusions

Optimal analysis of biopsy specimens for a problem of inflammatory diarrhea implies:

- That the pathologist receives a appropriate set of samples:
  - A full colon and ileum if possible
  - A colon alone in cases of fulminant colitis

- A good knowledge of the basic histologic features

- Interpretation of these features in a context of appropriate clinical information

- Optimally in close collaboration with the clinician

- A simple microscopic assessment is not sufficient for a precise diagnosis (in approximately 10-20% of cases)
Inflammatory diarrhea

Height surface epithelial cells
Cellularity (foamy cells)

Colitis
Neutrophils = active disease

Endoscopic sample

Normal architecture
Increased cellularity

Upper lamina propria
Infections
Drugs

IBD

focal
diffuse

Adult
Young
Adult untreated
Adult treated
Young

Ulcerative colitis
Crohn
IBDU (CD or UC)

IBDU (ulcerative colitis)

IBD in remission
Post surgery ...

Abnormal architecture

Increased cellularity

IBD

No increased cellularity

Indeterminate colitis
Colitis of known type
(CD or UC)
Colitis with some features of CD
Colitis not classifiable with available material

Surgical sample

Liver disease

Increased cellularity

Normal architecture

Increased cellularity

Adult
Young
Adult treated
Young