THE HISTOPATHOLOGICAL DIAGNOSIS OF THE TERMINAL ILEUM BIOPSY

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Normal small intestine
Variations

Duodenum
Ileum
Proliferative compartment

Normal variations

Ileal biopsy in IBD

- Ileum / jejunum / duodenum

- Ileum:
  Increased number of goblet mucous cells in villi
  Villi: shorter / finger-like
  - Proximal segments are of greater importance for nutrient digestion and transport
  - Proximal segments: more cells, greater absorptive surface area
  - Proximal segments: higher villus / crypt cell ratios

Prominent lymphoid tissue
**Peyer’s patches**  (lympho-epithelial complexes)  
**Normal structure**

First description **1677**

Diffusely present along the small intestine: antimesenteric

Numbers
- 24 weeks: +/- 45
- 12 year: +/- 305
- 20 year: +/- 200
- 95 year: +/- 100

Composition
Epithelial cells
  - M cells
  - FAE cells
Lymphoid components
  - Subepithelial mixed zone
  - Follicles

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**Normal ileum**  
**Peyers patches**

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NODULAR LYMPHOID HYPERPLASIA

Common in children and adolescents

Defensin5 expression in ileum
Decreased expression of human defensins 5 & 6 in ileum in CD Wehkamp et al Gut 2004; 53: 1658
NOD2 expression in Paneth cells Gastroenterology 2003
IBD or not

Clinical situations
Lesions of colon and ileum
Isolated ileitis

- Overview of historical and more recent studies
- Histopathological features for the diagnosis of Crohn’s disease
- Backwash ileitis
- Differential diagnostic cases
- The challenge of isolated ileitis

Overview of historical and more recent studies
The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn's disease

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Studies to determine the diagnostic value of ileoscopy and biopsy are not available. In an attempt to clarify the role of this technique in the diagnosis of intestinal Crohn's disease, 110 patients with a radiological diagnosis of inflammatory disease of the terminal ileum were examined in a prospective study. Suspcion of Crohn's disease was rejected in 28 patients. In 18 patients the terminal ileum was normal, while 10 patients had lymphoid nodular hyperplasia. Endoscopic lesions with a predictive value of 0.56 were found in 25 of 48 patients with the final diagnosis of Crohn's disease. Diagnostic granulomas were only found in 4 patients, but lesions consistent with Crohn's disease were present in the pathology sections of 17 patients. It was concluded that ileoscopy with biopsy is a valuable tool in the diagnosis of inflammatory ileal disease and can provide useful information about the nature and extent of the inflammation.

FINAL DIAGNOSIS :
A. PATIENTS STUDIED BY ENDOSCOPY (n=110)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>CROHN'S DISEASE</td>
<td>49</td>
<td>44.5</td>
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<tr>
<td>ACUTE AND CHRONIC INFECTIOUS ILEITIS</td>
<td>8</td>
<td>7.2</td>
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<td>ASPECIFIC ILEITIS</td>
<td>23</td>
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<td>BACKWASH ILEITIS</td>
<td>2</td>
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<tr>
<td>NODULAR LYMPHOID HYPERPLASIA</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>NORMAL TERMINAL ILEUM</td>
<td>18</td>
<td>16.3</td>
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Studies concerning biopsies of terminal ileum
I : History (1985)

Ileal biopsy in IBD

• Endoscopy of the terminal ileum:
  – Successful 72% 400 / 555
  – Not successful 8% 42
  – Not tried 11% 63
  – Inadequate cleaning 9% 50

• Ileoscopy valuable findings:
  29.5% 118 / 400
  abnormal: 5% 20 / 400

• In neoplastic diseases the diagnostic yield is unrewarding

(Börsch, Schmidt, Dis Col Rect, 1985)

Studies concerning biopsies of terminal ileum
I : History

Ileal biopsy in IBD

• n = 2324 consecutive ileocolonoscopies
• n = 1648 (> 70%) normal

Cuvelier, De Vos Acta Gastroenterol, 1995
Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of IBD?
Geboes e.a. Am J Gastroenterol 1998; 93; 201

Ileal biopsy: indication IBD

- 257 consecutive patients with clinical signs/suspicion of IBD in whom ileoscopy with biopsy was performed

Ileal biopsy: indication for ileocolonoscopy

- Chronic diarrhoea
- Acute diarrhoea
  - Severe
  - > 2 weeks
  - Blood loss +/−
  - Fever
  - Malaise
- Abdominal pain
- Abnormal ileal radiology
More recent studies


- Current theorized etiologies of this phenomenon, including subclinical Crohn's disease, nonsteroidal anti-inflammatory drugs, and spondylarthropathies.
More recent studies

• The diagnostic value of endoscopic terminal ileum biopsies.  
  McHugh e.a. Am J Gastroenterol 2007; 102: 1084  
  – We retrospectively reviewed 414 consecutive patients with terminal ileal biopsies.  
  – Biopsy of endoscopically normal mucosa is unlikely to yield diagnostically useful information, and is not encouraged as routine. However, when “ileitis,” ulcers, or erosions are identified, biopsies can be very helpful.  
  • Ileitis when it is not Crohn’s disease.  
  – Ileitis may be caused by a wide variety of other diseases.  
  – These include infectious diseases, spondyloarthopathies, vasculitides, ischemia, neoplasms, medication-induced, eosinophilic enteritis, and others.  
  – The diagnosis of the specific etiology is suggested by a detailed history and physical examination, laboratory testing, and ileocolonoscopy and/or radiologic data.  
  – Ileitis associated with spondylarthropathy or nonsteroidal anti-inflammatory drugs is typically subclinical and often escapes detection unless further testing is warranted by symptoms.

Isolated active ileitis

• Typical CD in 8/28 pts (27%)  
• 40 pts : no lesions in a median follow up of 3.2 yrs (82% NSAIDs)  
  – Lengeling e.a Clin Gastroenterol Hepatol. 2003;
Isolated active ileitis (IAI)
S. O’Donnell (Dublin)

- 63 patients with IAI retrospectively identified
- Repeat endoscopy
- Serum analysis for ANCA, anti-OmpC, ASCA IgA, ASCA IgG, anti-Cbir
- Result
  - No significant difference in the prevalence of antibodies between IAI cases and healthy controls
  - Look for genetic changes NOD2
  - Endoscopy follow up in 43 pts
    - 6/43 (14%) : definite Crohn’s disease
    - 18/43 (42%) : normal
    - 11/43 (26%) : persistent IAI

Conclusion

Ileoscopy is useful in carefully selected patients
Histopathological features for the diagnosis of Crohn’s disease

Crohn’s disease
Features useful for a precise diagnosis

Ileal biopsy in IBD

- Morphologic parameters: epithelium
  - Architecture:
    - Villi
    - Crypts
    - Shape / size
    - Branching
  - Cells:
    - Villous enterocytes
      - Shape
      - Tall columnar
      - Cuboidal
      - Flattened
      - Mucin production normal
    - Crypt cells
      - Mitosis
      - Paneth cells (location)
Active inflammation or not
Hypercrinia

Hypercrinia – Mucin preservation and relapse

Ileum – Distinctive mucosal features
Increased proportion of goblet cells within the epithelium (Segal & Petras, in: Histology for Pathologists, 1992, p547-)
Ratio Goblet cells/absorptive enterocytes 1/1
Hypercrinia
Increased number of goblet cells
Hypercrinia – Mucin preservation and relapse
Geboes et al unpublished

Material & Methods
71 pts operated for Crohn's disease
22 pts endoscopy at 12 months after surgery
12 pts endoscopy between 12 and 36 months
37 pts endoscopy > 36 months

Results
18/22 endoscopic recurrence / 55.6% hypercrinia
5 pts ratio goblet cells/enterocytes > 50%
5 pts ratio > 75%
10/12 recurrence / 60% hypercrinia
31/37 recurrence / 67.7% hypercrinia

Histopathology and relapse
Inflammation 2 (early postoperative lesions)

Eosinophils
Eosinophilic infiltration may occur in the neoterminal ileum within a few weeks of resection. Rutgeerts et al Gut 1984; 25: 665
Mucosal expression of interleukin 5 (IL-5) an important eosinophilic activating factor is increased (in association with prominent eosinophilic infiltration) in early recurrence. Dubucquoi et al Gut 1995; 37: 242
Masterson, unpublished results

- Utilizing a spontaneous eosinophilic Crohn’s-like disease murine model, it has been shown that there is an association between progression of ileitis and remodelling over the time course of 40 weeks.

- Eosinophilia correlated significantly with:
  - increased histological inflammatory indices ($R^2=0.86$; $P<0.05$).
  - Ileitis and remodelling were characterised by thickened muscularis propria, goblet cell hyperplasia, villus blunting and
  - molecular evidence of remodelling including increased expression of fibronectin (24.5 fold, $P<0.001$ (40 weeks)).

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**Ileal biopsy in IBD**

- Mucoid metaplasia
- Pseudopyloric gland metaplasia
- Ulcer associated cell lineage (UACL)

- Re-epithelialisation - regeneration subsequent to ulceration
Mucoid metaplasia

Not specific
Statistically most common in Crohn's disease

OTHER FEATURES

Granulomas

Lymphatics
Granulomas

Not specific
Diagnosis of Crohn's disease in association with other lesions
Frequency of finding: 3 – 56% for endoscopic samples
Highest frequency: children
Active inflammation – chronic inflammation - dilated lymphatics

Lymphatics and Crohn's disease
Dilated mucosal lymphatics

Increased numbers
Early lesions in Crohn’s disease


Summit lesion : usually associated with inflammation! Maunoury e.a. Endoscopy 2000; 32: 700-5
Early Mucosal Lesions in Crohn’s disease

3 : Epithelial patchy necrosis
or microulceration (loss of 1 – 6 epithelial cells)
4 : Naked surface of the dome area overlying a lymphoid follicle (with loss of M cells)
5 : Aphthoid ulcer
   Overlying a lymphoid follicle
   Or not

Backwash ileitis
Backwash ileitis & Ulcerative colitis

- Ileal lesions in continuity with colonic lesions
- Histology
  - Diffuse inflammation
  - Regular shortening of villi
- Disease activity correlates with level of cecal disease
- Frequency decreases
- Pathogenesis?
  - Terminology dates from barium enemas, when ileocecal valve was opened

Backwash ileitis
Goldstein & Dulsi Am J Clin Pathol 2006; 126:365
DIFFERENTIAL DIAGNOSTIC ISSUES

Other infections
  - Self-limited infections
  - Chronic infections

Mimics of IBD
  - NSAIDS
  - Ileitis and spondylarthropaty
  - Tumor associated lesions
    - Primary
    - Metastatic

Granulomas

Not specific
Diagnosis of Crohn's disease in association with other lesion

Yersinia
MIMICS OF IBD
NSAIDS
ILEITIS AND SPONDYLARTHROPATY
TUMOR ASSOCIATED LESIONS
PRIMARY
METASTATIC
VASCULITIS

NSAIDs
Tumor associated lesions

Patients are usually older

Spondylarthropathy
Associated lesions

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)
Female patient  
°1944  
Clinical History  
Stenosis of a renal artery and the celiac trunk  
Arterial hypertension  
Migraine  
Treatment: Cafergot, omeprazole, tiberal, plavix (clopidogrel)  
Current complaints: headache and diarrhea  
Endoscopy: Ischemia?  
> normal aspect

Microscopic ileocolitis (1008693)
Microscopic colitis
Histology – Small Intestine

Duodenal abnormalities in up to 70% (7% antiendomysial antibodies)
Ileal abnormalities in up to 15%
Primary ileal villous atrophy

Endometriosis
**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)

**Isolated ileitis**

**Challenges**

- NSAIDs ulc
- Adhesion
- Vascular diseases
- Infections
- Tumors:
  - neuroendocrine tumor of ileum
  - Metastasis
- Elderly patients; with a history of joint lesions
- Abdominal surgical history
- General symptoms/systemic disease
- General symptoms
- No features of
  - Age of the patient
  - No malabsorption in clinical chemistry
  - Short history
Miscellaneous

Athmospheric/food additives dust

Particularly in macrophages associated with Peyer’s patches (situated in the base) in the small intestine
In stroma
Appearance: dark brown or black (pigment rich in aluminium, silicon and titanium)
Frequency 34/42 (over 6 yrs of age) (Shepherd e a Hum Pathol 1987; 18: 50)
Sampling through M cells
Powell e.a. Gut 1996; 38: 390

Miscellaneous

Ileum – Deposition of iron
Miscellaneous

Bile pigment (ileum)

Miscellaneous

Waldenström’s Macroglobulinemia
Staining for kappa light chain