THE PATHOLOGY AND SIGNIFICANCE OF ILEITIS

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Normal small intestine

Variations

- The ileum constitutes 2/5ths of the small intestine
- **The wall** is thinner
- **Mesenteric fat** is abundant
- More vascular loops
- More **Goblet** cells
- Adult ileal mucosal **stem cells** might be different from stem cells in other areas, for instance by inducing bile acid uptake and expression of the IBAT protein (Middendorp e.a. Stem cells 2014)
- **Lymphoid tissue**
- Small intestinal tissue macrophages are different from those in the colon
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
Peyer’s patches (lympho-epithelial complexes)

Normal structure

First description 1677

Diffusely present along the small intestine: antimesenteric

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

Composition
Epithelial cells
  M cells
  FAE cells
Lymphoid components
  Subepithelial mixed zone
  Follicles
NODULAR LYMPHOID HYPERPLASIA

Common in children and adolescents
Ileitis : IBD or not?

- Indications for biopsy : overview of historical and recent studies

Clinical situations

Isolated ileitis

Lesions of colon and ileum

- The challenge of isolated ileitis
- Histopathological features for the diagnosis of Crohn’s disease
- Backwash ileitis
- Other causes of ileitis : differential diagnostic issues
- Miscellaneous
Studies concerning biopsies of terminal ileum

History (1984-1995)

The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn’s disease

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

- Ileoscopy valuable findings:
  - Abnormal: 5% (29.5% of 118/400)

- In neoplastic diseases the diagnostic yield unrewarding

(Börsch, Schmidt. Dis Col Rect. 1985)

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

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

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>43 %</td>
<td>111</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>25 %</td>
<td>63</td>
</tr>
<tr>
<td>ASLC (infectious type)</td>
<td>12 %</td>
<td>30</td>
</tr>
<tr>
<td>Inflammation (unclassified)</td>
<td>12 %</td>
<td>30</td>
</tr>
<tr>
<td>Ischemic disease</td>
<td>4 %</td>
<td>10</td>
</tr>
<tr>
<td>Non-specific ulceration (Bauhin)</td>
<td>2 %</td>
<td>5</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>1 %</td>
<td>3</td>
</tr>
<tr>
<td>Drug induced</td>
<td>1 %</td>
<td>2</td>
</tr>
<tr>
<td>Adhesions</td>
<td>1 %</td>
<td>2</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>&lt; 1 %</td>
<td>1</td>
</tr>
</tbody>
</table>
More recent studies


Etiologies of this phenomenon, include subclinical Crohn's disease, nonsteroidal anti-inflammatory drugs and spondylarthropathies


- 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 may be caused by a wide variety of other diseases.
- These include infectious diseases, spondyloarthropathies, 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.
Conclusion

Ileoscopy with biopsy is useful in carefully selected patients.

These include: inflammatory diarrhea; presence of endoscopic lesions; anaemia...
Isolated active ileitis (IAI)

• Typical CD in 8/28 pts (27%)

• 60 patients with IAI (O’Donnell et al 2013)
  – Repeat endoscopy
  – Serum analysis for ANCA, anti-OmpC, ASCA IgA, ASCA IgG, anti-Cbir
  – Results
    • No significant difference in the prevalence of antibodies between IAI cases and healthy controls
    • Endoscopy follow up in 43 pts
      – 6/43 (14%) : definite Crohn’s disease
      – 18/43 (42%) : normal
      – 11/43 (26%) : persistent IAI

• 40 pts : no lesions in a median follow up of 3.2 yrs (82% NSAIDs)
  – Lengeling e.a Clin Gastroenterol Hepatol. 2003;
Isolated ileitis

Challenges

• NSAIDs ulc

• Adhesion

• Vascular diseases

• Infections

• Tumors  Mass lesions :
  – 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
Histopathological features for the diagnosis of Crohn’s disease

Early lesions

Diagnostic lesions

- Based on multiple samples
- Heterogeneity of villous architecture
Early lesions in Crohn’s disease are associated with inflammation

The only exception (?) are damage and rupture of small capillaries underneath intact epithelium with subsequent loss of surface epithelial cells (the summit lesion)

Although even then inflammation is common
Maunoury, e.a. Endoscopy 2000; 32: 700
Early Mucosal Lesions in Crohn’s disease

2: Epithelial patchy necrosis or microulceration (loss of 1 – 6 epithelial cells)

3: Naked surface of the dome area overlying a lymphoid follicle (with loss of M cells)

4: Aphthoid ulcer
   Overlying a lymphoid follicle
   Or not
Diagnostic lesions

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

- Not specific
- Diagnosis of Crohn’s disease in association with other lesion
- Frequency of finding: 3 – 56% for endoscopic samples
- Highest frequency: children
Lymphatics and Crohn’s disease

Dilated mucosal lymphatics

Increased numbers
Lymphangiogenesis
Active inflammation – chronic inflammation - dilated lymphatics
Active inflammation (relation with treatment)
Histopathology and relapse
Inflammation (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
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

Endoscopic recurrence
  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
Terminal Ileitis & Ulcerative colitis
Backwash ileitis?

Definition (historical)
- Backwash: reflux of contents due to inflammation-induced malfunction of ileocecal valve
- Associated with pancolitis

Terminal ileitis in UC with mildly active disease!?
Terminal - Backwash ileitis
Goldstein & Dulsi Am J Clin Pathol 2006; 126:365

- Ileal lesions in continuity with colonic lesions
- Histology
  - Diffuse inflammation
  - Regular shortening of villi
- Correlation with extent of disease
- Disease activity correlates with level of cecal disease
- Frequency decreases
- Pathogenesis?
  - Terminology dates from barium enemas, when ileocecal valve was opened
  - Primary manifestation of the disease (would explain terminal ileitis in patients with mildly active disease)
DIFFERENTIAL DIAGNOSTIC ISSUES

Other infections
  Self-limited infections
    Viral gastroenteritis occurs especially in the pediatric age group.
    Bacterial pathogens are Shigella, Salmonella, Campylobacter, Yersinia, Escherichia coli, Clostridium difficile
  Chronic infections
    Mycobacteria

Mimics of IBD
  NSAIDS
  Other DRUGS
  Ileitis and spondylarthropaty
  Tumor associated lesions
    Primary
    Metastatic
Granulomas

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

Yersinia
Tuberculosis
MIMICS OF IBD

NSAIDS

OTHER DRUGS
ILEITIS AND SPONDYLARTHROPATHY
TUMOR ASSOCIATED LESIONS
PRIMARY
METASTATIC

VASCULITIS

NSAIDs
Clinical history
Tumor associated lesions
Patients are usually older
Spondylarthropathy
Associated lesions
Other Drugs

• Olmesartan medoxomil, an angiotensin II receptor antagonist
  – 25 cases out of a series of 12,935 or 0.19%.
  – Lesions are observed usually one to two years after the start of the medication.
  – Woman are slightly more affected.
  – Increased collagen deposition can be noted.
• Ipilimumab, a humanized monoclonal antibody developed to reduce and overcome cytotoxic T-lymphocyte antigen 4 (iatrogenic autoimmune enteropathy)
• Imatinib mesylate (treatment of GIST)
• Mycophenolate mofetil (MMF)
Olmesartan
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 (clodipogrel)

Current complaints: headache and diarrhea

Endoscopy: Ischemia? > normal aspect
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)
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

Systemic mastocytosis
Behçet disease
Can involve Ileum (& colon)

Behçet
- Ulcers on opposite side of the mesentery
- Unrelated to the site of M-cells or lymphoid tissue
- Changes limited to mucosa adjacent to ulcers

Endoscopic biopsies can hardly differentiate

Crohn
Ulceration in small bowel

- Isolated non-specific ulcer
  - Rare (40/100,000 pts)
  - Mainly ileum (at 100 cm of the valve)
  - Male preponderance

- Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)

- Idiopathic chronic ulcerative enteritis (ICUE)

- Chronic non-specific multiple ulcers of the intestine
  - Four candidate mutations in the solute carrier organic anion transporter family, member 2A1 (SLCO2A1) gene, encoding a prostaglandin transporter, were identified (Hosoe et al. J Crohn Colitis 2017)
Conclusions

• Ileal biopsies can provide information in patients with endoscopic features of ileitis and clinical symptoms of (inflammatory diarrhea)
• Isolated active ileitis is not always Crohn’s disease
• So-called backwash ileitis is not yet well understood
• Various conditions may induce either isolated ileitis or ileitis in association with colitis
• These include infections, drugs but also less common conditions (mass lesions...)

Iatrogenic autoimmune-like enteritis Pathophysiology

• CTLA-4 is expressed on regulatory T cells and patients receiving treatment with anti-CTLA-4 show abnormal numbers of regulatory T cells in intestinal biopsies
• Enterocytes can express MHC class II (like normal antigen presenting cells) but lack expression of the costimulatory molecules (CD80 and CD86) needed to activate naïve T-cell
  – Yet, under certain conditions, they can express other costimulatory markers such as PD-L1 (programmed cell death)
  – Blockade of PD-L1, the ligand of PD-1, leads to the development of autoimmune enteritis.
• AIE-like enteritis can develop following severe depletion of gut microbiota from antibiotic therapy, consistent with the idea that commensal microorganisms play an important role in regulating gut immunity