Pathology of Inflammatory Bowel Disease

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Cord Langner MD
Institute of Pathology
Medical University Graz / Austria
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Outline

- ECCO ESP Consensus on the Histopathology of Inflammatory Bowel Disease in 2013
  - Ulcerative Colitis
  - Crohn’s Disease
  - Microscopic Colitis
- Difficulties in IBD Diagnosis and Differential Diagnosis
- Take Home Message
CONSENSUS/GUIDELINES

European consensus on the histopathology of inflammatory bowel disease

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The histopathological approach to inflammatory bowel disease: a practice guide

Cord Langner · Fernando Magro · Ann Driessen · Arzu Ensari · Gerassimos J. Mantzaris · Vincenzo Villanacci · Gabriel Bechenu · Paula Borracho Nunes · Gieri Cathomas · Walter Fries · Anne Jouret-Mourin · Claudia Mescoli · Giovanni de Petris · Carlos A. Rubio · Neil A. Shepherd · Michael Vieth · Rami Eliakim · Karel Geboes

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Abstract Inflammatory bowel diseases (IBDs) are lifelong disorders predominantly present in developed countries. In their pathogenesis, an interaction between genetic and environmental factors is involved. This practice guide, prepared on behalf of the European Society of Pathology and the European Crohn’s and Colitis Organisation, intends to provide a thorough basis for the histological evaluation of resection specimens and biopsy samples from patients with ulcerative colitis or Crohn’s disease. Histopathologically, these diseases are characterised by the extent and the distribution of mucosal architectural abnormality, the cellularity of the lamina propria and the cell types present, but these features frequently overlap. If a definitive diagnosis is not possible, the term indeterminate colitis is used for resection specimens and the term inflammatory bowel disease unclassified for biopsies. Activity of disease is reflected by neutrophil granulocyte infiltration

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Basic Principles of Histological IBD Diagnosis

- Analysis of **multiple biopsies** allows a correct diagnosis of inflammatory bowel disease in 66-75% of newly diagnosed patients.

- Providing additional **endoscopic and clinical data** to the pathologist increases the diagnostic accuracy, allowing a final diagnosis in more than 90% of cases.

- The histological features useful for a diagnosis of inflammatory bowel disease may be grouped into four categories:
  - Mucosal architecture
  - Lamina propria cellularity
  - Neutrophil polymorph infiltration
  - Epithelial abnormality
Basic Principles of Histological IBD Diagnosis

- Abnormalities in crypt architecture
  - Crypt distortion
  - Crypt branching
  - Crypt atrophy (shortening)
  - Surface epithelium irregularities (pseudovillous change)
  - Reduced crypt density

- Abnormalities in crypt architecture are particularly pronounced in ulcerative colitis (57-100% of cases), but may also occur in Crohn’s disease (27-71% of cases)
Basic Principles of Histological IBD Diagnosis

- Lamina propria cellularity
  - Transmucosal increase of inflammatory cells
  - Basal plasmacytosis
  - Non-necrotic epithelioid cell granulomas are present in approximately 20-50% of cases with Crohn’s disease (DD cryptolytic granulomas in ulcerative colitis)

- Neutrophils (cryptitis / crypt abscess formation) = markers of disease activity

- Epithelial changes: epithelial damage and mucin depletion (at active sites), metaplastic changes (markers of chronicity)
Ulcerative Colitis: Key Histologic Features

- Diffuse (continuous) mucosal disease that begins in the rectum and spreads variably to the proximal colon (worse distally)
- Severe diffuse mucosal architectural abnormalities (crypt atrophy and distortion, decreased crypt density)
- Severe diffuse transmucosal increase of (predominantly mononuclear) inflammatory cells with basal plasmacytosis
- Epithelial abnormalities, such as surface epithelial damage and mucin depletion as well as Paneth cell metaplasia (in biopsies obtained distal to the hepatic flexure)
- Tissue fragments both within the same biopsy and within separately submitted specimens tend to show the same degree of inflammation
- Rare epithelioid cell granulomas, related to ruptured crypts
Ulcerative Colitis
Crohn’s Disease: Key Histologic Features

- Segmental (discontinuous) transmural disease (“skip lesions” with fissures, fistulae) with variable rectal involvement and variable disease severity (worse proximally)
- Focal (discontinuous) crypt architectural abnormalities (focal crypt atrophy and distortion)
- Focal (discontinuous) inflammation (focal mononuclear expansion of the lamina propria, focal cryptitis). Focal or patchy inflammation may be observed in biopsies submitted from different parts of the bowel or may be present within tissue fragments of the same biopsy, not rarely within a single biopsy specimen
- Aphthous erosions/ulcers and deep fissures, any location
- Epithelioid cell granulomas (not crypt related) in approximately 20% of mucosal biopsies (up to 50% in resections)
- Transmural lymphoid aggregates as well as fibromuscular obliteration and nerve fiber hyperplasia in the submucosa on surgical specimens
Crohn’s Disease
Upper Gastrointestinal Tract in Crohn’s Disease
Outline

- ECCO ESP Consensus on the Histopathology of Inflammatory Bowel Disease in 2013
  - Ulcerative Colitis
  - Crohn’s Disease
  - Microscopic Colitis
- Difficulties in IBD Diagnosis and Differential Diagnosis
- Take Home Message
Selected Difficulties in Histological IBD Diagnosis

- Ulcerative colitis and Crohn’s disease show overlapping morphological features, and a precise diagnosis may be difficult, if not impossible in 10-15% of cases.

- **Terminology:** Indeterminate colitis (on resection specimens) or IBD unclassified, IBDU (on biopsies).

- In fact, there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn’s disease.
## Selected Difficulties in Histological IBD Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Infectious colitis</th>
<th>UC active phase</th>
<th>UC in remission</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt architectural abnormalities</td>
<td>- / (+)</td>
<td>+++</td>
<td>+/- +</td>
<td>(+)</td>
</tr>
<tr>
<td>Metaplastic Paneth cells / mucin depletion</td>
<td>-</td>
<td>++</td>
<td>++ / (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Mononuclear cells ↑</td>
<td>(+)</td>
<td>+++</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Granulomas / giant cells</td>
<td>(+)</td>
<td>(+)</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Continous morphologic changes</td>
<td>(+)</td>
<td>+++</td>
<td>++ / (+)</td>
<td>-</td>
</tr>
<tr>
<td>Discontinous morphologic changes</td>
<td>+</td>
<td>-</td>
<td>- / (+)</td>
<td>++</td>
</tr>
</tbody>
</table>
Selected Difficulties in Histological IBD Diagnosis

- Ulcerative colitis and Crohn’s disease show overlapping morphological features, and a precise diagnosis may be difficult, if not impossible in 10-15% of cases.
- **Terminology:** Indeterminate colitis (on resection specimens) or IBD unclassified, IBDU (on biopsies).
- In fact, there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn’s disease.
- Differential diagnosis between ulcerative colitis and Crohn’s disease may also be challenging when patients are under therapy: mucosal healing in ulcerative colitis may cause discontinuous inflammation (and “rectal sparing”).
active colitis

- normal architecture
  - increased cellularity
    - upper lamina propria
    - basal lamina propria

- abnormal architecture
  - increased cellularity
    - no increased cellularity

infections / drugs

inflammatory bowel disease (IBD)

IBD in remission

diffuse
- adult
- young

focal
- adult untreated
- young untreated
- adult / young treated

ulcerative colitis

Crohn’s disease

IBD unclassified (IBDU)
Crohn’s disease: distribution within the GI tract

- Stomach: microscopic lesions in 50-75%
- Isolated large bowel CD in 15-25%
- Isolated small bowel CD in 30-35%
- CD affecting both small and large bowel in 40-50%
Characteristics of colonic Crohn’s disease

Clinical and pathological analysis of colonic Crohn’s disease, including a subgroup with ulcerative colitis-like features

Genevieve Soucy¹, Helen H Wang², Francis A Farraye³, Jason F Schmidt⁴, Alton B Farris⁵, Gregory Y Lauwers³, Sandra R Cerda³, Kleaithis G Dendrinos⁶ and Robert D Odze⁷

¹Department of Pathology, Centre Hospitalier Universitaire de Montreal, Montreal, Quebec, Canada; ²Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³Department of Gastroenterology, Boston Medical Center, Boston, MA, USA; ⁴Department of Pathology, Methodist Health System, Dallas, TX, USA; ⁵Department of Pathology, Massachusetts General Hospital, Boston, MA, USA; ⁶Department of Gastroenterology, Internal Medicine Group, Cheyenne, WY, USA and ⁷Department of Pathology, Brigham and Women’s Hospital, Boston, MA, USA
Characteristics of colonic Crohn‘s disease

- Older age (compared with patients with CD in both small and large bowel)
- Higher percentage with total, subtotal, and left-sided colonic involvement
- The rule of thumb “inflammation in the proximal colon > inflammation in the distal colon” is no longer valid
- Less strictures and stenoses
- In 15% of cases „ulcerative colitis-like Crohn‘s disease“ (with inflammation restricted to the mucosal layer)
Characteristics of colonic Crohn’s disease

Table 1 Clinical features of patients with colonic Crohn's disease

<table>
<thead>
<tr>
<th>Features</th>
<th>Isolated colonic Crohn’s</th>
<th>Ileocolonic Crohn’s</th>
<th>Total</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 73</td>
<td>N = 45</td>
<td>N = 118</td>
<td></td>
</tr>
<tr>
<td>M/F ratio</td>
<td>29/44 (1:1.5)</td>
<td>21/24 (1:1.1)</td>
<td>50/68 (1:1.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>37</td>
<td>26</td>
<td>33</td>
<td>0.003&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of colitis (years)</td>
<td>7.7</td>
<td>13.0</td>
<td>9.7</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Extent of colitis</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>12/73 (16%)</td>
<td>2/45 (4.4%)</td>
<td>14/118 (12%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Subtotal</td>
<td>14/73 (19%)</td>
<td>3/45 (6.7%)</td>
<td>17/118 (14%)</td>
<td></td>
</tr>
<tr>
<td>Left sided</td>
<td>33/73 (45%)</td>
<td>5/45 (11%)</td>
<td>38/118 (32%)</td>
<td></td>
</tr>
<tr>
<td>Right sided</td>
<td>10/73 (14%)</td>
<td>20/45 (44%)</td>
<td>30/118 (25%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4/73 (5.5%)</td>
<td>15/45 (33%)</td>
<td>19/118 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>Mild</td>
<td>14/73 (19%)</td>
<td>5/45 (11%)</td>
<td>19/118 (16%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>23/73 (32%)</td>
<td>10/45 (22%)</td>
<td>33/118 (28%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>32/73 (44%)</td>
<td>25/45 (56%)</td>
<td>57/118 (48%)</td>
<td></td>
</tr>
<tr>
<td>Fulminant</td>
<td>4/73 (5.5%)</td>
<td>5/45 (11%)</td>
<td>9/118 (7.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total colectomy</td>
<td>16/73 (22%)</td>
<td>3/45 (6.7%)</td>
<td>19/118 (16%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>13/73 (18%)</td>
<td>2/45 (4.4%)</td>
<td>15/118 (13%)</td>
<td></td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>31/73 (42%)</td>
<td>11/45 (24%)</td>
<td>42/118 (36%)</td>
<td></td>
</tr>
<tr>
<td>Right hemicolectomy</td>
<td>11/73 (15%)</td>
<td>25/45 (56%)</td>
<td>36/118 (31%)</td>
<td></td>
</tr>
<tr>
<td>Ileal pouch–anal anastomosis</td>
<td>20/73 (27%)</td>
<td>10/45 (22%)</td>
<td>30/118 (25%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean follow-up interval (years)</td>
<td>5.1</td>
<td>6.9</td>
<td>5.9</td>
<td>0.10&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Soucy et al. Mod Pathol 2012
### Characteristics of colonic Crohn’s disease

<table>
<thead>
<tr>
<th>Features</th>
<th>Colonic Pathology</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolated colonic Crohn’s</td>
<td>Ileocolonic Crohn’s</td>
</tr>
<tr>
<td></td>
<td>N = 73</td>
<td>N = 45</td>
</tr>
<tr>
<td><strong>(a) Major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricture/stenosis</td>
<td>19/72 (26%)</td>
<td>29/45 (58%)</td>
</tr>
<tr>
<td>Adhesions</td>
<td>10/72 (14%)</td>
<td>25/45 (56%)</td>
</tr>
<tr>
<td>Creeping fat</td>
<td>19/72 (26%)</td>
<td>15/45 (33%)</td>
</tr>
<tr>
<td>Fistula tract</td>
<td>9/73 (12%)</td>
<td>11/45 (24%)</td>
</tr>
<tr>
<td>Sinus tract</td>
<td>21/73 (29%)</td>
<td>11/45 (24%)</td>
</tr>
<tr>
<td>Segmental disease</td>
<td>30/70 (43%)</td>
<td>30/45 (67%)</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>18/73 (25%)</td>
<td>6/45 (13%)</td>
</tr>
<tr>
<td><strong>Microscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal &gt; distal (severity)</td>
<td>13/73 (18%)</td>
<td>20/45 (44%)</td>
</tr>
<tr>
<td>Skip lesions (absolute)</td>
<td>10/73 (14%)</td>
<td>9/45 (20%)</td>
</tr>
<tr>
<td>Granulomas</td>
<td>39/73 (53%)</td>
<td>22/45 (49%)</td>
</tr>
<tr>
<td>Transmural lymphoid aggregates</td>
<td>49/73 (67%)</td>
<td>35/45 (78%)</td>
</tr>
<tr>
<td>Fissuring ulcers</td>
<td>29/73 (40%)</td>
<td>20/45 (44%)</td>
</tr>
<tr>
<td><strong>(b) Minor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submucosal fibrosis</td>
<td>64/73 (88%)</td>
<td>36/45 (80%)</td>
</tr>
<tr>
<td>Neural hypertrophy</td>
<td>31/73 (42%)</td>
<td>17/45 (38%)</td>
</tr>
<tr>
<td>Muscularis mucosae hypertrophy</td>
<td>28/73 (38%)</td>
<td>22/45 (49%)</td>
</tr>
<tr>
<td>Muscularis propria hypertrophy</td>
<td>35/73 (48%)</td>
<td>15/45 (33%)</td>
</tr>
<tr>
<td>Plexitis</td>
<td>23/73 (32%)</td>
<td>9/45 (20%)</td>
</tr>
<tr>
<td>Perivascular lymphoid aggregates</td>
<td>30/72 (42%)</td>
<td>10/45 (22%)</td>
</tr>
<tr>
<td>Serositis</td>
<td>35/73 (48%)</td>
<td>29/45 (64%)</td>
</tr>
<tr>
<td>Pyloric metaplasia</td>
<td>2/50 (4.0%)</td>
<td>30/45 (67%)</td>
</tr>
</tbody>
</table>

Soucy et al. Mod Pathol 2012
Differential Diagnosis

- Prolonged infection
  In early-onset IBD (2-6 weeks after the first symptoms), the classical histological features may not be fully established yet

- Superinfection in established IBD
  - Bacterial infection
  - Virus infection, particularly CMV

- Segmental colitis associated with diverticulosis/diverticulitis (SCAD) or diverticular disease-associated colitis (DAC)
  - Chronic colitis with crypt architectural abnormalities, mixed inflammatory infiltrate, cryptitis and crypt abscess formation as well as basal plasmacytosis and occasional Paneth cell metaplasia in the interdiverticular luminal mucosa
  - Biopsies proximal and distal to the involved segment should be normal
Segmental colitis associated with diverticulosis (SCAD)
Segmental colitis associated with diverticulosis (SCAD)
Segmental colitis associated with diverticulosis (SCAD)

<table>
<thead>
<tr>
<th>Histopathological feature</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mononuclear cell increase in lamina propria</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Cryptitis</td>
<td>23 (100)</td>
</tr>
<tr>
<td>With crypt abscesses</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Basal lymphoid aggregates</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Distortion of crypt architecture</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Surface epithelial sloughing</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Granulomatous cryptitis</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Villiform configuration of mucosa</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Pattern of inflammation</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Focal</td>
<td>5 (22)</td>
</tr>
</tbody>
</table>

**TABLE 1.** Histopathological features of 23 cases of diverticular disease-associated colitis

Segmental colitis associated with diverticulosis (SCAD)

- **Definition and pathogenesis**
  - Chronic colitis in a segment with diverticulosis („idiosyncratic“ reaction), no extension of (peri)diverticulitis into the mucosa
  - Prevalence 1-3% of cases with (pseudo)diverticulosis

- **Differential diagnosis**
  - IBD: endoscopically it may look like UC (30-40%) or CD (10%), always try to get biopsy material from the descending colon and the rectum (which should be normal)
  - Be careful with a diagnosis of CD in this situation (when no other segment of the GI tract is involved): “healing of CD” was achieved in 23 of 25 cases after segmental resection!
  - Erosions and/or ulcerations with granulation tissue
    - CMV (patient history / immunohistochemistry / quantitative PCR)
    - NSAIDs (right > left, looks more “ischaemic”)

Diverticulosis in IBD

- 1037 pts colitis / proctitis
  - 311 pts proctitis
    - 726 pts colitis
      - 365 pts CU
        - 182 pts under 50 / short disease duration
          - 183 pts CU
      - 314 pts CD
        - 209 pts under 50 / short disease duration
          - 105 pts CD
      - 47 pts indeterminate
        - 21 pts under 50 / short disease duration
          - 26 pts indeterminate

Lahat et al. Inflamm Bowel Dis 2007
Diverticulosis in IBD

314 IBD patients

- Diverticulosis in 11 (3.5%) patients

1023 Age-matched screening colonoscopies

- Diverticulosis in 152 (15%) patients

183 pts CU
105 pts CD
26 pts indeterminate
Take Home Message

- Accurate histological diagnosis of IBD is based upon the analysis of multiple biopsies from different segments of the large bowel (in combination with endoscopic and clinical data)

- **Main histological categories**
  - Alteration in mucosal architecture
  - Increased lamina propria cellularity
  - Neutrophil polymorph infiltration
  - Epithelial abnormality (defects, metaplastic changes)

- **Differential diagnosis**
  - Ulcerative colitis vs. Crohn’s disease (IBD unclassified)
  - Prolonged infection
  - Segmental colitis associated with diverticulosis/diverticulitis (SCAD) or diverticular disease-associated colitis (DAC)
Thank you very much for your attention!

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