Case 1
19-year-old male with known lactose intolerance and travellers diarrhoea

Patient history
19-year-old male with known lactose intolerance. He has just returned from a one-month-trip to France. Already on the second day of that trip sudden onset crampy abdominal pain and diarrhoea (3-4x per day). Since then no full recovery, ongoing mild diarrhoea and flatulence.

First endoscopy grossly normal. Biopsies from the duodenum show intraepithelial lymphocytosis and mild villous atrophy, compatible with Marsh type 3a of celiac disease (external diagnosis). Gliadin and tissue transglutaminase antibodies negative. Gluten-free diet without effect. Progressed weight loss.

Second endoscopy again grossly normal. New biopsies are taken from the duodenum.
Diagnosis:

Lymphocytic enteritis in giardiasis
(full recovery after therapy with metronidazole)

Patient history

27-year-old female with diagnosis of “inflammatory bowel disease” (symptoms since eight years).

Until today no definitive diagnosis of Crohn’s disease or ulcerative colitis (“IBD unclassified”).

Ongoing therapy with 5-ASA, no immunosuppression.

Upon endoscopy “moderate inflammatory changes, more diffuse than focal, throughout the entire colon”, the terminal ileum is normal.

The slide shows step biopsies obtained from the large bowel.

Histology and Giardiasis

- In 95% of cases entirely normal mucosa (always look for giardiasis before signing out a duodenal biopsy as normal!)
- In 5% of cases abnormal or inflamed mucosa
  - Increased cellularity in the lamina propria with lymphoid follicles and neutrophils (→ bacterial superinfection?)
  - Intraepithelial lymphocytosis with varying degrees of villous atrophy (usually mild to moderate)

<table>
<thead>
<tr>
<th>Location</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>438</td>
<td>77.2%</td>
</tr>
<tr>
<td>Jejunum</td>
<td>111</td>
<td>19.3%</td>
</tr>
<tr>
<td>Stomach</td>
<td>37</td>
<td>10.1%</td>
</tr>
<tr>
<td>Duodenum and stomach</td>
<td>24</td>
<td>4.5%</td>
</tr>
<tr>
<td>Duodenum and jejunum</td>
<td>9</td>
<td>1.6%</td>
</tr>
<tr>
<td>Jejunum and stomach</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>Stomach and stomach</td>
<td>1</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Oberhuber et al. Scand J Gastroenterol 1997
Diagnosis:
Crohn’s disease of the large bowel

Case 3
47-year-old male with chronic inflammatory bowel disease

Patient history
47-year-old male with “known inflammatory bowel disease” (no information regarding Crohn’s disease or ulcerative colitis is provided clinically), currently “in remission”.

The surveillance endoscopy shows pseudopolyps from the ascending colon to the sigmoid colon, the rectum mucosa is normal upon gross inspection.

The slide shows biopsies obtained from the sigmoid colon.
Diagnosis:
Ulcerative colitis (in remission, under therapy)
Basic Principles of Histologic 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 Histologic 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 Histologic 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 (indicating 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

... this is not mild chronic „unspecific“ 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

Ulcerative colitis vs. Crohn’s disease: histology

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt architectural irregularity</td>
<td>Diffuse (continuous)</td>
<td>Focal (discontinuous)</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Absent, except with regional crypts</td>
<td>Uncommon, present</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Absent, except with regional crypts</td>
<td>Uncommon, present</td>
</tr>
<tr>
<td>Location of inflammation</td>
<td>Transmural</td>
<td>Transmural</td>
</tr>
<tr>
<td>Sexuality</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Lymphoid aggregates</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Absent, except with regional crypts</td>
<td>Uncommon, present</td>
</tr>
<tr>
<td>Mucosal hyperplasia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Peptic ulcer oesophagus</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Perforation</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Papillary glands</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Absent, except with regional crypts</td>
<td>Uncommon, present</td>
</tr>
<tr>
<td>Transmural lymphoid aggregates</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Fibromuscular obliteration</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Nerve fiber hyperplasia</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

ESP/ECCO Consensus

European consensus on the histopathology of inflammatory bowel disease


...available at www.medunigraz.at/ENGIP

Discussion

Case 2

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

Wheelock, S. Crohn’s disease: macroscopy

- Ulcerative colitis
  - Location: Gl tract
  - Bears: especially colon
  - Blood: not exudate in bowel biopsy
  - Colitis: not present
  - Rectum: not involved
  - Diffuse Gl tract
  - Ulcers: superficial ulcers
  - Inflammatory polyps: absent
  - Skip lesions: absent
  - Colonic lesions: absent
  - Deep colon: absent
  - Fissures: absent
  - Fistulae: absent
  - Mucosal edema: normal
  - Thicker than the wall: normal
  - Fibrin: normal
  - Skins: normal

- Crohn’s disease
  - Location: Gl tract
  - Bears: not exudate in bowel biopsy
  - Blood: not exudate in bowel biopsy
  - Colitis: not present
  - Rectum: not involved
  - Diffuse Gl tract
  - Ulcers: segmental (discontinuous)
  - Inflammatory polyps: present
  - Skip lesions: absent
  - Colonic lesions: present
  - Deep colon: present
  - Fissures: present
  - Fistulae: present
  - Mucosal edema: present
  - Thicker than the wall: normal
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Characteristics of colonic Crohn’s disease

- Distribution within the GI tract
  - Stomach: microscopic lesions in 50-75%
  - Isolated small bowel CD in 15-25%
  - Isolated large bowel CD in 30-35%
  - CD affecting both small and large bowel in 40-50%
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)

Selected Difficulties in Histologic 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 histologic feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histologic observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn’s disease

Discussion Case 3

Selected Difficulties in Histologic IBD Diagnosis

Crypt architectural abnormalities

- Infectious colitis: UC active phase: UC in remission: Crohn’s disease
  - / (+) +++ (+) (+)

Metaplastic Paneth cells / mucin depletion

- UC active phase: UC in remission: Crohn’s disease
  - ++ / (+) (+)

Mononuclear cells

- UC active phase: UC in remission: Crohn’s disease
  - +++ (+) (+)

Neutrophils

- UC active phase: UC in remission: Crohn’s disease
  - +++ (+) (+)

Granulomas / giant cells

- UC active phase: UC in remission: Crohn’s disease
  - (+) (+) (+)

Continuous morphologic changes

- UC active phase: UC in remission: Crohn’s disease
  - (+) (+) (+)

Discontinuous morphologic changes

- UC active phase: UC in remission: Crohn’s disease
  - * * * (*)

Differential Diagnosis of Inflammatory Bowel Diseases

Table 1: Clinical features of patients with ulcerative colitis-like Crohn’s disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intra-mural</th>
<th>Intraductal</th>
<th>Both</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>48/100 (48%)</td>
<td>30/100 (30%)</td>
<td>78/100(78%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>3.4*</td>
<td>3.4</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of colonic Crohn’s disease
Selected Difficulties in Histologic 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 histologic feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histologic 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”).

Pitfalls in the diagnosis of inflammatory bowel disease

- Ulcerative colitis with Crohn’s disease-like features
  - Discontinuous inflammation and (relative) “rectal sparing” in children and adolescents and under therapy (in these cases do not change an established diagnosis of UC)
  - Aphthous or fissural ulceration
  - Inflammation within the terminal ileum (usually short segment, in continuity with large bowel inflammation)
  - Granulomas (‘cryptolytic’ granulomas with foreign body reaction)
  - Rarely involvement of the upper GI tract, particularly in children and adolescents

- Crohn’s disease with ulcerative colitis-like features
  - Continuous or pancolitis
  - Superficial (or mucosal) colitis

- DD: other colitides
  - SCAD (case 7)
  - Microscopic colitis with IBD-like features
  - NSAIDs-induced colitis with IBD-like features
  - Prolonged infection (DD early IBD)
Diagnosis:
Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)

Differential diagnosis of small bowel ulceration (and stenosis)

- Crohn’s disease
- Drugs, in particular NSAIDs
- Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)
- Ulcerative jejunoileitis with celiac disease or sprue-like intestinal disease
- Tumours
  - Malignant lymphoma
  - Other tumours
- Ischemia (e.g. vasculitis, hypercoagulability)
- Infectious enteritis (e.g. tuberculosis, Case 5)

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)

- Clinical presentation
  - Obstructive enteropathy (e.g. in conjunction with weight loss, anaemia)
  - Steroid-responsive, chronic and/or relapsing course (often surgical therapy)
  - No NSAIDs (patients with CMUSE are usually younger than patients using NSAIDs)
- Macroscopy
  - Multifocal ulceration and short-segment stenoses (mean 8, range 2-25), particularly in the jejunum and the upper half of the ileum
- Histology
  - Chronic superficial ulceration and stenosis (fibrosis, metaplasia)
  - Unspecific inflammation (no granulomas)
  - Obstructive vessel changes (“vasculopathy”)
Patient history

48-year-old male in severely reduced general and nutritional condition is referred to the hospital with acute abdomen. No definitive explanation on CT scan.

Immediate laparatomy. Intraoperatively, the wall of the terminal ileum is thickened, and the serosal surface is reddened, partly covered by a yellowish exudate. Ileocaecal resection is performed.

Grossly, the resection specimen shows marked edema and confluent ulceration of the ileal mucosa. The slide shows the appendix.

CMUSE vs. Crohn’s disease

<table>
<thead>
<tr>
<th></th>
<th>CMUSE</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic inflammatory response (pathological laboratory data)</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Localisation and distribution</td>
<td>jejunum &gt; ileum (restricted to the small bowel)</td>
<td>ileum &gt; jejunum (often involvement of the large bowel and upper GI tract)</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>rare</td>
<td>typical</td>
</tr>
<tr>
<td>Type of ulceration</td>
<td>superficial, shallow</td>
<td>fissural, transmural</td>
</tr>
<tr>
<td>Fistulas</td>
<td>absent</td>
<td>typical</td>
</tr>
<tr>
<td>Histology</td>
<td>granulomas</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>lymphoid follicles</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>metaplasia</td>
<td>possible</td>
</tr>
</tbody>
</table>

CMUSE = burned-out Crohn’s disease?
Freeman HJ. World J Gastroenterol 2009

ENGIP Case of the Month November 2013

Case 5

48-year-old male with acute abdomen
Diagnosis:
Appendiceal tuberculosis

TBC: Ziehl–Neelsen stain

Mycobacterium tuberculosis complex-PCR positive!

Differential Diagnosis
- Crohn’s disease
- Yersiniosis
- Other forms of granulomatous inflammation
  - Sarcoidosis
  - Immune defects
    - Chronic granulomatous disease
    - Common variable immunodeficiency (CVID)
  - Vasculitis
  - Granulomas associated with neoplasia ("sarcoid reaction")
  - Drug reactions
  - Foreign body granulomas

Tuberculosis in the gastrointestinal tract

- Pathogenesis
  - *Mycobacterium bovis*: transmission to humans by infected cow milk (developing countries with no pasteurisation of milk)
  - *Mycobacterium tuberculosis*: active lung tuberculosis → swallowing of infected material from the lung (typical in Western countries)

- Clinical presentation of abdominal (gastrointestinal) tuberculosis
  - Unspecific symptoms: abdominal pain, weight loss, anaemia, lymph node enlargement, (sub)ileus

17-year-old male with recurrent appendicitis

Case from Josef Rüschoff, Kassel, Germany

TBC: Histology

Mycobacterium tuberculosis complex-PCR positive!

Tuberculosis in the gastrointestinal tract

- Distribution
  - Predominantly ileocaecal region including appendix (90%)
  - Ascending colon > duodenum/stomach > distal colon

- Macroscopy
  - Ulcers, typically above Peyer plaques and lymphoid follicles, inflammatory pseudotumours, scars / strictures

- Histology
  - Granulomatous (transmural) inflammation with central fibrillogranular necrosis, mucosal ulceration

- Diagnosis
  - Compatible H&E morphology, histochemistry (Ziehl-Neelsen stain), molecular analysis (Mycobacterium tuberculosis complex-PCR)

17-year-old male with recurrent appendicitis

Case from Josef Rüschoff, Kassel, Germany
22 cases with interval appendectomy (mean 58 days, range 30-95), treated with antibiotics and/or drainage

**Case 6**

24-year-old female with purulent sinusitis and bloody diarrhoea

**Patient history**

24-year-old female with purulent sinusitis which is treated with amoxycillin.

Five days later bloody diarrhoea. Colonoscopy shows segmental colitis with haemorrhage and marked mucosal friability in the ascending colon and right transverse colon.

Stool testing for *Shigella sp.*, *Salmonella sp.*, *Campylobacter sp.*, and Yersiniosis is negative.

The slide shows biopsies obtained from the inflamed colonic mucosa in the right colon.

**Diagnostic test:**

Stool testing for pathogenic bacteria (incl. *Klebsiella oxytoca*)

**Histopathology of Interval (Delayed) Appendectomy Specimens**

Strong Association With Granulomatous and Xanthogranulomatous Appendicitis

Guangming Gao, M.D., and Joel K. Greenon, M.D.

The American Journal of Surgical Pathology, 27(1), 114-123, 2003

<table>
<thead>
<tr>
<th>Group</th>
<th>Total no. of cases</th>
<th>Granulomas [no. (%)]</th>
<th>Colonic changes [no. (%)]</th>
<th>Xanthogranulomatous inflammation [no. (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>22</td>
<td>13 (59.1)</td>
<td>11 (50.0)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>AA</td>
<td>44</td>
<td>3 (6.8)</td>
<td>1 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*IA, interval appendectomy; AA, acute appendectomy.*
**Diagnosis:** Segmental penicillin-induced haemorrhagic colitis

**Epidemiology and forms of antibiotic-associated diarrhoea**
- Incidence of antibiotic-associated diarrhoea 15-25%
- Antibiotics with high likelihood
  - Ampicillin/Amoxicillin
  - Cephalosporin
  - Clindamycin
- Clinical presentation / diseases
  - Antibiotic-associated diarrhoea without colitis
  - Pseudomembranous colitis (→ **non-bloody** diarrhoea)
  - Segmental penicillin-induced haemorrhagic colitis (→ **bloody** diarrhoea)

**Colitis caused by bacterial infections**
- Acute infectious („self-limiting“) colitis
  - Salmonella enteritidis
  - Campylobacter jejuni / Campylobacter coli
  - Yersinia enterocolitica
- Bacterial colitis under therapy with antibiotics → alteration of the normal bacterial flora (reduction of competing bacteria leads to extensive growth of certain bacteria)
  - Clostridium difficile → Pseudomembranous colitis
  - Klebsiella oxytoca → Segmental penicillin-induced haemorrhagic colitis

**Acute infectious („self-limiting“) colitis**

**Histology**
- Preserved crypt architecture (no other signs of chronic inflammation, e.g. basal plasmacytosis)
- Presence of neutrophils in the (superficial) lamina propria (disproportionate inflammation)
- Neutrophils within crypt epithelium and/or crypt lumen (cryptitis, crypt abscess), only rarely within the surface epithelium (differential diagnosis antibiotic-associated colitis)
- Mucosal haemorrhage, possible erosions/ulcerations
- Possible pitfall: the inflammation may be diffuse or patchy/discontinuous (differential diagnosis Crohn’s disease)
Histology of pseudomembranous colitis

- **Type 1 lesion**
  - Inflammatory changes restricted to the interglandular surface epithelium and immediately subjacent lamina propria
  - Focal epithelial necrosis or irregularity, together with the presence of polymorphs, nuclear dust, and eosinophilic exudate in the lamina propria
  - Small luminal showers of fibrin and polymorphs spaying out from these foci ("volcano-like lesions")

- **Type 2 lesion**
  - Group of disrupted glands, distended by mucin and polymorphs, usually with loss of the superficial half of the epithelial lining.
  - On top a cloud of epithelial debris, fibrin, mucus, and polymorphs, 'the pseudomembrane'.

- **Type 3 lesion**
  - Complete structural necrosis of the mucosa with thick covering of fibrin, mucus, and inflammatory debris

Price & Davies, J Clin Pathol 1997

---

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- **Type 3 lesion**
  - Complete structural necrosis of the mucosa with thick covering of fibrin, mucus, and inflammatory debris

Price & Davies, J Clin Pathol 1997

---

Patient history

68-year-old female with known sigmoid diverticulosis. Recurrent episodes of left-sided lower abdominal discomfort and changing stool habits (obstipation and mild diarrhoea).

Upon endoscopy moderate redness, small mucosal ulcerations, and small pseudopolyps within the sigmoid colon, while all other parts of the colon (including the rectum) are normal.

The slide shows biopsies obtained from the inflamed colonic mucosa in the sigmoid colon. Inflammatory bowel disease?
Diagnosis:
Segmental colitis associated with diverticulosis (SCAD)
**Diverticulosis in IBD**

1037 pts colitis / proctitis

- 311 pts proctitis
- 726 pts colitis
- 365 pts CU
- 314 pts CD
- 47 pts indeterminate

182 pts under 50 / short disease duration
- 26 pts under 50 / short disease duration
105 pts CD
- 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

Lahat et al. Inflamm Bowel Dis 2007

**Cytomegalovirus infection**

- **Pathogenesis**
  - Primary or secondary immunological incompetence
  - Iatrogenic immunological incompetence: therapy of autoimmune diseases (IBD, but also rheumatic diseases), after organ transplantation

- **Morphology**
  - Crypt architecture (depending on the underlying disease) usually not or only insignificantly altered
  - Erosion / ulceration with (prominent) granulation tissue
  - Nuclear (and cytoplasmic) inclusions ("owl’s eye" appearance)
  - Ancillary techniques: CMV immunohistochemistry or quantitative (!) PCR

**CMV in IBD**


**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)
    - NSAR (right > left, looks more 'ischaemic')

Patient history

In 10/2012 skin rash and diarrhoea.
Colonoscopy: ulcerations of the ileum mucosa, severe colitis, predominantly in the right colon.
The slide shows biopsies obtained from the ascending colon.

Case 8

62-year-old female with diarrhoea after allogeneic stem cell transplantation
Clinical classification of GvHD

<table>
<thead>
<tr>
<th>Time of onset (days after HSCT)</th>
<th>Features of acute GvHD</th>
<th>Features of chronic GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GvHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>„Classic” acute GvHD ≤ 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent or late-onset GvHD &gt; 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic GvHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>„Classic” chronic GvHD No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome between acute and chronic GvHD No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Washington & Jagasia. Human Pathology 2009

GvHD within the gastrointestinal tract

- Epidemiology
  - Skin GvHD in approx. 10%
  - Gastrointestinal GvHD in approx. 4 - 13%

- Technical considerations
  - H&E step sections (minimum 8 levels; PAS, Giemsa)
  - CMV immunohistochemistry (minimum one location, particularly mucosal defects)

- Distribution within the gastrointestinal tract
  - In the whole GI tract: biopsies from the lower gastrointestinal tract have a higher sensitivity, PPV, and NNV than biopsies from the upper gastrointestinal tract

Ross et al., Am J Gastroenterol 2008

Washington & Jagasia. Human Pathology 2009

GvHD within the gastrointestinal tract

- Histology (no clear dichotomy between acute and chronic GvHD)
  - Apoptosis („exploding crypt cell“, mainly crypt base, minimum one apoptosis per biopsy specimen)
  - Crypt loss: notable discrepancy between epithelial loss and only sparse primarily mononuclear inflammation, residual cystic microcrypts
  - Other (possible) features: intraepithelial T-lymphocytes (>5 IEL/100 epithelial cells), eosinophils, foam cells, pericapillary haemorrhage

- Differential diagnosis
  - CMV infection
  - Other infections (e.g. cryptosporidium)
  - Drugs (e.g. mycophenolate mofetil (MMF), NSAIDs / chemotherapy, including conditioning regimens within 20 days after HSCT)
  - Ischemia

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Recommendations for pathology reporting in GvHD

<table>
<thead>
<tr>
<th>Not GvHD</th>
<th>No evidence of GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible GvHD</td>
<td>Cases with evidence of GvHD but other possible explanations (e.g. MMF colitis, apoptotic bodies only near to CMV inclusions)</td>
</tr>
<tr>
<td>Consistent with GvHD</td>
<td>Clear histological evidence of GvHD but with mitigating factors, such as limited sample, minimal findings (rare apoptotic bodies)</td>
</tr>
<tr>
<td>GvHD</td>
<td>Unequivocal evidence of GvHD</td>
</tr>
</tbody>
</table>

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Diagnosis:
Graft-versus-host disease (GvHD)
Grade 3 according to Lerner et al. (optional)
Grading of acute GvHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isolated apoptotic epithelial cells, without crypt loss</td>
</tr>
<tr>
<td>2</td>
<td>Loss of isolated crypts without loss of contiguous crypts</td>
</tr>
<tr>
<td>3</td>
<td>Loss of two or more contiguous crypts</td>
</tr>
<tr>
<td>4</td>
<td>Extensive crypt loss with mucosal denudation</td>
</tr>
</tbody>
</table>

Chemotherapy I (prostate cancer, 5-FU)

- **Mechanism of action**
  - Pyrimidine analog which works through irreversible inhibition of thymidylate synthase (antimetabolite function). Interrupting the action of this enzyme blocks synthesis of the pyrimidine thymidine, which is a nucleoside required for DNA replication (→ activation of p53).

- **Histology**
  - Preserved mucosal architecture
  - Eosinophilia and vacuolisation of crypt epithelial cells
  - Cellular and nuclear atypia ("bizarre nuclei"), in case of ulceration identical atypia within the granulation tissue, preserved nuclear/cytoplasmic ratio
  - No (or only very limited) apoptoses
  - Reduced cellularity within the stroma (may appear almost "empty")

Chemotherapy II (prostate cancer, Taxane)

- **Mechanism of action**
  - Disruption of microtubule function (spindle poison), inhibition of mitosis → "frozen mitosis"

- **Histology**
  - Increased number of mitotic figures
  - Atypical mitoses ("ring mitoses")
  - Where? Principally in all tissues, particularly the regenerative zone (next to the stem cell niche), depending on tissue half time for self renewal; lower GI tract > upper GI tract (possible pitfall: intestinal metaplasia in chronic gastritis)

Chemotherapy I (colorectal cancer, 5-FU)

- **Mechanism of action**
  - Preserved mucosal architecture
  - Eosinophilia and vacuolisation of crypt epithelial cells
  - Cellular and nuclear atypia ("bizarre nuclei"), in case of ulceration identical atypia within the granulation tissue, preserved nuclear/cytoplasmic ratio
  - No (or only very limited) apoptoses
  - Reduced cellularity within the stroma (may appear almost "empty")

Chemotherapy II (prostate cancer, Taxane)

Lesson of the month

Possible pitfall in diagnostic: mitotic arrest of gastric epithelium after dextran sulfate therapy for hormone-refractory prostate cancer