Coeliac disease: the current role of pathology (I)

Luigi Terracciano
Coeliac Disease

- Coeliac disease (CD) is a gluten-sensitive enteropathy characterized by villous atrophy, which is reversed by gluten withdrawal
- Genetically susceptible individuals (99% HLA DQ2 or HLA DQ8)
- Classical presentation: Malabsorption, steatorrhea, weight loss or other signs of nutrient or vitamin deficiency, dermatitis herpetiformis
- Coeliac disease may be clinically occult and may not be detected until late adulthood
Coeliac Disease in Switzerland

- Coeliac disease is common in Switzerland
- Symptomatic CD 1 in 1,000 inhabitants
- Asymptomatic CD is still more common: prevalence of 0.75% in adolescents of Canton of St. Gallen

Rutz R, Swiss Med Wkly, 2002
Coeliac Disease

- NOT a histological diagnosis
- BUT histology is the gold standard and is required to support other features
  - Clinical history and symptomatology
  - IgA class: anti-gliadin antibodies
    - anti-endomysial antibodies (EMA)
    - anti-tissue transglutaminase antibodies (TTG)
  - HLA-DQ2 and/or DQ8
  - clinical recovery to gluten exclusion within weeks
  - gluten challenge
The morphologic spectrum of coeliac disease

• Shortened, widened villi or even flat mucosa

• Intraepithelial lymphocytosis ( > 20 IEL /100 enterocytes) CD3+ (>95%) / CD8+ (70-90%)
  \( \gamma\delta \) Tcell receptor is increased to >10%

• Hyperplastic crypts ( > 1 mitosis per crypt)

• Decreased enterocyte height, intracytoplasmic vacuolation, absence of brush-border
Gluten-Sensitive Enteropathy (Celiac Disease)
Controversies in Diagnosis and Classification

An Update on Celiac Disease Histopathology and the Road Ahead

Fei Bao, MD; Peter H. R. Green, MD; Govind Bhagat, MD

Arch Pathol Lab Med—Vol 136, July 2012

Arzu Ensari, MD, PhD

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| Table 2. Classification Schemes For Pathologic Evaluation of Gluten-Sensitive Enteropathy |
|-----------------------------------------------|----------------|----------------|----------------|
| Marsh, \textsuperscript{56} 1992               | Oberhuber et al, \textsuperscript{59} 1999 | Corazza & Villanaci, \textsuperscript{64} 2005 | “New” Proposal |
| Type 1                                        | Type 1         | Grade A        | Type 1         |
| Type 2                                        | Type 2         | Grade A        | Type 1         |
| Type 3                                        | Type 3A        | Grade B1       | Type 2         |
| Type 4                                        | Type 3B        | Grade B1       | Type 2         |
|                                               | Type 3C        | Grade B2       | Type 3         |
|                                               | Type 4         | obsolete       | obsolete       |
Old and New Classifications for Histopathologic Evaluation of Celiac Disease-Associated Mucosal Changes

<table>
<thead>
<tr>
<th>Marsh-Oberhuber Classification</th>
<th>Corazza-Villanacci Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Grade A</td>
</tr>
<tr>
<td>Type 2</td>
<td>Grade B1</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Grade B2</td>
</tr>
<tr>
<td>Type 3b</td>
<td>deleted</td>
</tr>
<tr>
<td>Type 3c</td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td></td>
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</tbody>
</table>
### Table 1
Criteria for Marsh-Oberhuber Stages of Celiac Disease

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Type 0</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3a</th>
<th>Type 3b</th>
<th>Type 3c</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEL count/100 epithelial cells</td>
<td>&lt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
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<tr>
<td>Crypts Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypertrophic</td>
<td>Normal</td>
<td>Hypertrophic</td>
<td>Normal</td>
<td>Hypertrophic</td>
</tr>
<tr>
<td>Villi Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

IEL, intraepithelial lymphocyte.

### Table 2
Criteria for Corazza Stages of Celiac Disease

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Nonatrophic A</th>
<th>Atrophic B1</th>
<th>Atrophic B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraepithelial lymphocytosis</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Villi Normal</td>
<td>Normal</td>
<td>Still detectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Marsh-Oberhuber equivalent</td>
<td>Types 1 and 2</td>
<td>Types 3a and 3b</td>
<td>Type 3c</td>
</tr>
</tbody>
</table>
What is „Normal“?

The presence of at least 3-4 consecutive villi with a normal villous to crypt ratio

Biopsy specimen must be properly oriented

Villous height : crypt depth
Subepithelial collagen plate
IELs /100 epithelial cells

3:1 to 5:1 (duodenum ➔ ileum)
<10µ
<25
Intra-epithelial lymphocytic infiltrate

- The majority of normal subjects have less than 20 ly / 100 epithelial cells
- 25-29 ly / 100 epithelial cells: borderline
- > 30 ly / 100 epithelial cell: pathological!
- To stain or not to stain for CD3?
  - Only in suspected cases
  - More to highlight the distribution pattern than the actual counts
Currently, the normal upper limit of IELs is accepted as 20 Ly /100 enterocytes.

Normal “Decrescendo” pattern of IELs
Type 1: Increased IELs, normal architecture

Tip-heavy lymphocytosis

Loss of “Decrescendo” pattern of IELs along sides of villi in normals


Goldstein NS. *Histopathology* 2004; 44: 199-205

VILLOUS TIP COUNT
METHOD: >6 PER 20 ENTEROCYTES IN 5 VILLI
(Biagi F: *JCP* 2004; 57:835)
Type 2: PARTIAL OR SUBTOTAL VILLOUS ATROPHY
Type 3: TOTAL VILLOUS ATROPHY
Small-bowel mucosa showing abnormal enterocytes in the superficial epithelium and inflammation in the lamina propria comprising numerous neutrophils with cryptitis and crypt abscess

Brown J, Am J Clin Pathol 2012; 138:42
Thick patchy subepithelial collagen band (< 5µm, in 36-60% of cases) associated with total villous atrophy of the small bowel-bowel mucosa

Brown J, Am J Clin Pathol 2012; 138:42
### Differential Diagnosis of Celiac Disease with normal villous architecture and increased IEL counts

- Food hypersensitivity: cow’s milk, soy, fish, rice, chicken, etc
- Peptic ulcer disease
- Helicobacter pylori-associated gastroduodenitis
- Drugs: NSAIDs, proton-pump inhibitor
- Infections: viral enteritis, *Giardia* organisms, *Cryptosporidium* organisms
- Immune dysregulation: rheumatoid arthritis, Hashimoto thyroiditis, SLE, autoimmune enteropathy
- Immunodeficiency: common variable immune deficiency
- GVHD
- Inflammatory bowel disease
- Bacterial overgrowth
- Lymphocytic and collagenous colitis
- Irritable bowel syndrome

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Bao F, Arch Pathol Lab Med 2012; 136: 735-745
<table>
<thead>
<tr>
<th>Differential Diagnosis of Celiac Disease with villous atrophy with or without increased IEL counts</th>
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</thead>
<tbody>
<tr>
<td>Infections: tropocal sprue</td>
</tr>
<tr>
<td>Refractory sprue</td>
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<tr>
<td>Collagenous sprue</td>
</tr>
<tr>
<td>Immune dysregulation: autoimmune enteropathy</td>
</tr>
<tr>
<td>Immunodeficiency: common variable immunodeficiency</td>
</tr>
<tr>
<td>GVHD</td>
</tr>
<tr>
<td>Inflammatory bowel disease: Crohn disease</td>
</tr>
<tr>
<td>Drugs: mycophenolate, olmesartan, colchicine</td>
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<tr>
<td>Chemoradiation therapy</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td>Eosinophilic enteritis</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

Bao F, Arch Pathol Lab Med 2012; 136: 735-745
Problems in Coeliac Disease

• Patchiness
  – Recommend a minimum of four 3mm biopsies from D2 or beyond
  – Performing a biopsy only in the duodenal bulb may be a source of error, or may at least greatly reduce the sensitivity of the examination

  (≈10% of children and ≈ 2% of adults will have flat duodenal bulb biopsies in the presence of normal biopsies in the more distal duodenum)

Pais WP, Gastrointest Endosc 2008; 67:1082-7
High Density Intraepithelial Lymphocyte Enteropathy

- Coeliac disease (Type 1)
- Potential coeliac disease (*latent* and *preclinical* disease)

- Asymptomatic 1st degree relatives of coeliacs
  - 15% have flat mucosa
  - 25% have intraepithelial lymphocytosis

- Dermatitis herpetiformis
  - 70% have flat mucosa (half asymptomatic)
  - 40% have intraepithelial lymphocytosis
High Density Intra-epithelial Lymphocyte Enteropathy

• Brisbane - 100 cases
  – 12% coeliac disease
  – 10% NSAIDs
  – 20% Proton pump inhibitors
  – 20% Autoimmune disease
  – 25% self-limiting
  – 10% had HP gastritis
  – 5% had lymphocytic colitis

Brown I, Clouston AD (IAP Congress 2004)
What we have to consider if recurrent symptoms occur in established Coeliac Disease?

- Poor compliance with a strict GFD (may be unintentional)
- Wrong initial diagnosis (consider other causes of villous atrophy)
- Second cause of symptoms
e.g. microscopic colitis
- Superimposed complication
e.g. collagenous sprue
References


